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TREATMENT OF INCAPACITATED EUTHYROID CARDIAC PATIENTS BY PRODUCING HYPOTHYROIDISM WITH RADIOACTIVE IODINE*

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THE purpose of this communication is to summarize our experience since November, 1947, in treating 37 patients with chronic heart disease by lessening the cardiac work through inducing hypothyroidism with radioactive iodine (I^{131}).[1-3] Our efforts have proceeded in four main directions: the clinical appraisal of the therapeutic value of the procedure; study of possible deleterious radiation effects; establishment of criteria for the proper selection of patients; and investigation and control of the secondary consequences of the hypothyroid state. Although final conclusions concerning these problems must await the results obtained over many years in various clinics, it may be helpful to describe our experience to date.

The 37 patients with chronic heart disease who are the basis of this report were carefully selected from a much larger number of patients with heart disease observed at the Beth Israel Hospital. Each patient was believed to be euthyroid on the basis of clinical criteria, the basal metabolic rate, serum cholesterol, tracer doses of I^{131} [4, 5] and, in some instances, the serum protein-bound iodine. Most of the 37 patients were chronic invalids confined to a bed-and-chair existence or were unable to undertake more than slight effort without experiencing angina pectoris or recurrence of congestive failure. Every patient had been incapacitated for many months or years in spite of having received the usual accepted medical therapeutic measures. Their clinical course had been stationary or only slightly worse during the months immediately prior to treatment; consequently any striking improvement could be confidently attributed to the radioactive-iodine treatment.

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Results in 17 Patients with Angina Pectoris Observed for Ten to Twenty-Six Months in the Hypometabolic State

Of the 26 patients with angina pectoris, 17 have been observed in the hypometabolic state from ten to twenty-six months (average, seventeen and a half months). In the remaining 9 patients, the period of follow-up is too brief for definitive clinical evaluation; the early results in these patients appear favorable and in accordance with our over-all experience. The severity of cardiac involvement is reflected by the fact that 20 attacks of acute myocardial infarction had occurred in these 17 patients prior to treatment. The ages of the patients ranged from 38 to 72 years. The etiology of the angina pectoris was coronary arteriosclerosis in all cases. Arterial hypertension with blood pressures ranging from 160–200/90–120 was present in 8.

Of these 17 patients with angina pectoris the therapeutic result has been decidedly worth while in 11 (Fig. 1). In each instance, the patient has been able to undertake activities hitherto impossible for many months or years. In 7 of these 11 patients, the results have been rather remarkable. Either angina pectoris has been abolished or only occasional attacks have occurred despite greatly increased activity. The duration of angina pectoris before I^{131} treatment in these 11 patients was from one to ten years and averaged four-and-a-half years. Four of these patients (Cases 1, 2, 5 and 22) are now gainfully employed, whereas prior to treatment they had been largely incapacitated for years because of inability to undertake minimal effort without symptoms. The following cases are illustrative.

CASE REPORTS

CASE 1. J. L. (B. I. H. 69433), a 41-year-old man, was referred through the courtesy of Dr. J. F. F. Riseman. One year prior to I^{131} therapy attacks of substernal pressure on exertion and emotion were first noted, and an attack of acute myocardial infarction occurred eight months before treatment. He had been unable to work for the previous nine months and had been restricted largely to the house because walking even 100 ft. precipitated an attack. He was awakened by anginal attacks, often suffering three or four episodes nightly. He noted increasing dyspnea and used two pil-

lows. In the month prior to I^{131} therapy, he had used over 500 tablets of nitroglycerin. During his illness he had received theobromine sodium acetate, potassium iodide, sedatives, quinidine and atropine; nitroglycerin alone was of slight help. There was no history of arterial hypertension or of rheumatic or syphilitic infection.

Physical examination revealed entirely normal findings. The blood pressure was 110/80.

Laboratory examination revealed that the urine and blood were normal. On x-ray examination, the heart was normal

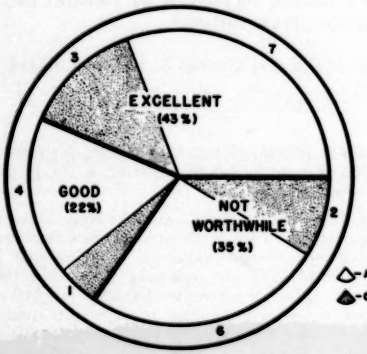

FIGURE 1. *Results in 23 Euthyroid Patients with Angina Pectoris and Congestive Failure Treated with* I^{131}.

in size and shape. The electrocardiogram was consistent with an old posterior infarct.

On April 27, 1948, he received 29 mc. of I^{131}.* Three additional doses of 43, 39 and 39 mc. were administered on July 23, August 13 and November 22, 1948, respectively (Fig. 2). Five weeks after the first dose of I^{131}, definite clinical improvement was noted, with disappearance of all but a few attacks of angina pectoris. The serum-cholesterol level had risen and clinical signs of hypothyroidism were present. During the next few weeks, anginal episodes reverted to the pretreatment severity and frequency; the basal metabolic rate and serum-cholesterol values had changed toward normal. Five weeks after the third dose, hypometabolism became evident and the patient experienced marked improvement. He was able to undertake much more effort although he used only approximately 8 nitroglycerin tablets per week. Five weeks after the fourth dose, complete disappearance of angina pectoris was observed. In repeated exercise-tolerance tests,[6] forty-five to fifty trips were performed without anginal pain; the patient stopped exercise at our request or because of fatigue. Repeated pretreatment exercise-tolerance tests averaged 30 trips and were invariably halted because of cardiac pain. He is gainfully employed, having worked eight hours a day for the past fifteen months, experiences no angina except on very strenuous exertion and is not troubled by symptoms of myxedema. On a daily dosage of 30 mg. of thyroid, the basal metabolic rate is maintained at −25 per cent; the serum cholesterol is 900 mg. per 100 cc.

CASE 19. L. A., a 67-year-old woman, had had angina pectoris for ten years. She was referred to this hospital through the courtesy of Dr. Paul D. White, who had observed the patient for five years. She had suffered 3 myocardial infarctions eight, five and one year prior to I^{131} therapy. During the four years prior to this treatment she was largely housebound and suffered attacks not only on effort but on excitement and at night. Despite marked limitation of activity, approximately 60 nitroglycerin tablets and frequent injections of Demerol were required each week.

On physical examination, the heart was enlarged to the left; the rhythm was regular; soft apical and basal systolic murmurs were audible. The blood pressure was 164/92. A small nodule was felt at the right lower pole of the thyroid. The basal metabolic rate was −5 per cent and the serum cholesterol 425 mg. per 100 cc. An electrocardiogram showed left-bundle-branch block.

I^{131} treatment was begun on April 18, 1949 (Fig. 3). Four doses totaling 84 mc. were administered. Striking improvement manifested by freedom from angina pectoris despite increased activity was first noted ten weeks after treatment and has been maintained during the last thirteen months. Two additional doses totaling 46 mc. were administered when hypometabolism diminished. During the past several months the basal metabolic rate has been maintained at −20 per cent and the serum cholesterol at approximately 460 mg. per 100 cc. On 6 mg. of thyroid daily, she experiences no discomfort from the hypometabolic state and has only

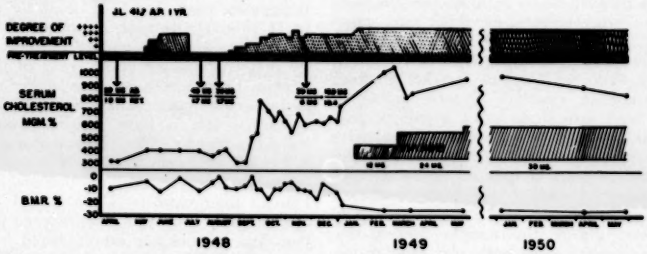

FIGURE 2. *Serum Cholesterol, Basal Metabolic Rate and Clinical Course in Case 1, after Administration of 4 Doses of* I^{131} *Totaling 150 mc.*

an occasional mild attack once in one or two weeks on overactivity.

Another patient, R. A., a 62-year-old bricklayer, had had severe angina pectoris for three years and had been invalided at home since acute myocardial infarction and pulmonary edema fourteen months before treatment. He suffered frequent attacks of paroxysmal nocturnal dyspnea. After three doses of I^{131} myxedema was produced, with complete remission of all cardiac symptoms. He has been maintained on 30 mg. of thyroid daily at a basal metabolic rate of −20 per cent

*The millicurie used in these studies conforms to the United States Bureau of Standards millicurie.

and a serum cholesterol level of 350 mg. per 100 cc. and is not troubled by symptoms of hypometabolism. He has been gainfully employed as a foreman of bricklayers, a position requiring considerable physical activity. Similar striking results have been obtained in four other patients.

In the remaining 6 of the 17 patients with angina pectoris, the therapeutic result has not been worth while (Fig. 1). Two of the 6 patients died, twelve and nineteen months after receiving treatment with I^{131} (Cases 10 and 11). In one case (Case 8), angina pectoris was relieved for six months

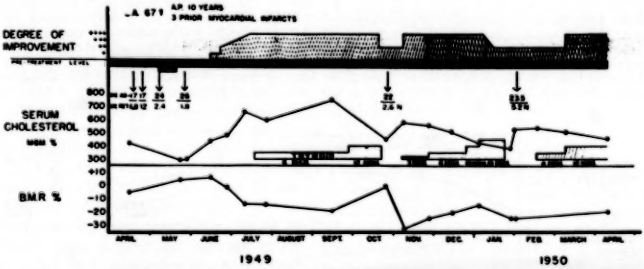

FIGURE 3. *Serum Cholesterol, Basal Metabolic Rate and Clinical Course in Case 19 after Administration of 6 Doses of I^{131} Totaling 130 mc.*

The millicuries retained after the last two doses, labeled N, represent the amount retained in the thyroid gland as measured by external counting.

but has relapsed to pretreatment status. In the other 5 patients, angina pectoris was definitely lessened when the patients exhibited the clinical and laboratory evidences of myxedema. It was impossible, however, to maintain the patients at such metabolic levels, because of the discomfort of myxedema. When thyroid was administered to ameliorate the discomfort of myxedema, attacks of angina pectoris occurred with sufficient frequency and severity to make us consider the result not worth while. The following case is illustrative.

CASE 8. M. H. (B. I. H. 72724), a 65-year-old housewife, received two doses of I^{131} totaling 75 mc., of which 21.2 mc. was retained in the body. She had had diabetes for twenty years and angina pectoris during the eighteen months before treatment. Acute myocardial infarction occurred one year before I^{131} treatment. Three months before treatment, examination in the Cardiac Clinic revealed frequent palpitation and attacks of angina pectoris 1 to 12 times daily on emotion or slight exertion and that were aggravated by cold and were of much greater frequency and severity than prior to the acute myocardial infarction. The average weekly requirement of nitroglycerin was 11 to 17 tablets.

The heart was enlarged; the sounds were of good quality and the rhythm regular. The blood pressure was 130/80.

On x-ray examination the heart was slightly enlarged and the lungs clear. Electrocardiographic findings were consistent with old posterior myocardial infarction and left-ventricular hypertrophy. The nonfasting serum cholesterol, observed three hours postprandially on a standard diabetic diet, averaged 360 mg. per 100 cc.

On November 6, 1948, the patient received 39 mc. and on January 21, 1949, 34 mc. of I^{131}. Ten weeks after the second dose, the patient experienced fewer and less severe episodes of squeezing precordial pain. Six weeks later, — four months after the second dose, — the patient noted further marked improvement and required nitroglycerin only once every two to three weeks. Furthermore, the urinary reductions of Benedict's solution were negative more frequently than before, and the daily dose of insulin was reduced from 56 units of protamine insulin and 20 of regular insulin to 50 units of protamine insulin and 12 of regular insulin. The serum cholesterol was 540 mg. per 100 cc. Although she was extremely grateful for the relief of angina the patient noted many symptoms of myxedema, which were ameliorated by ingestion of 24 mg. of thyroid daily. On this dosage she began to experience occasional mild episodes of angina pectoris, requiring 2 to 5 nitroglycerin tablets a week. After a remission of six months' duration she relapsed to the pretreatment level of angina. The serum cholesterol was 409 mg. per 100 cc.

Results in Six Patients with Congestive Failure Observed for Seven to Twenty-Six Months in the Hypothyroid State

Of the 11 patients with congestive failure, 6 have been observed in the hypometabolic state for six to twenty-six months (average, nineteen months). In the remaining 5, the period is too brief for clear evaluation of the therapeutic result. In 2 of the 6 patients the improvement has not been worth while. Four of the 6 patients who were in the hypometabolic state for six to twenty-six months showed worthwhile improvement. One of these patients (Case 16[3]), a 46-year-old woman with a past history of rheumatic heart disease and chronic congestive failure for seven years, was completely incapacitated at the time of the inception of hypometabolism. Congestive failure previously uncontrolled was markedly improved, in that dyspnea, orthopnea and paroxysmal nocturnal dyspnea were ameliorated with the occurrence of hypometabolism following treatment with I^{131}. She was able to do her housework, visit friends and lead a generally more active though still restricted regimen for two years. Two years after I^{131} treatment she died suddenly while asleep.

In three of the six patients, the improvement following I^{131} therapy has been striking. The relief from dyspnea, attacks of pulmonary edema and paroxysmal nocturnal dyspnea has been associated with objective evidences of diminution or disappearance of peripheral edema and of pulmonary congestion. The following case is illustrative.

CASE 15. M. G. (B. I. H. M1759), a 44-year-old man, had had arterial hypertension for nine years and two prior attacks of acute myocardial infarction. One and a half years before treatment, ankle edema and dyspnea appeared, the blood pressure was 230/120, a nonfunctioning kidney was demonstrated and a left nephrectomy was performed. The blood pressure was reported to have dropped to 114/70. Five months before entry he noted recurrence of ankle edema, increased weight and dyspnea. Despite a low-salt diet, digitoxin and mercurial diuretics, the dyspnea, orthopnea and intermittent edema became worse and he was hospitalized. On vigorous treatment with bed rest, low-salt diet, of the right leg. The dose of digitalis was increased, ammonium chloride and mercurial diuretics were again given and some improvement was noted. During the first two months after I^{131} treatment, the cholesterol decreased slightly from 278 to about 238 mg. per 100 cc. and then began to rise, reaching and remaining at a level of 500 mg. The patient's face became puffy and his hands cool and dry, but he experienced no symptoms of hypothyroidism. During this period of hypometabolism he demonstrated progressive improvement.

At the present time, eighteen months after induction of myxedema, he is able to undertake increased activity, including some carpentry and considerable walking, without developing dyspnea. Orthopnea, which formerly required 4 to 5 pillows, is no longer present. He sleeps on 1 pillow. The patient states that he has not felt this well in two years. Venous distention has diminished, and there is no peripheral edema. The lungs are clear to percussion and auscultation. Ascites, present at the time of treatment, did not recur after one paracentesis. Neither spleen nor liver is now palpable. The electrocardiogram is unchanged. Venous pressure is 55 mm. of water (compared to 260 mm. before treatment), the

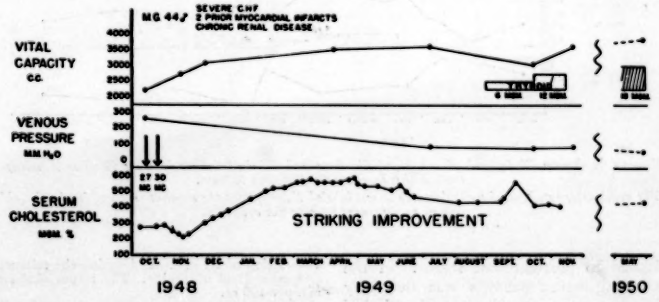

FIGURE 4. *Serum Cholesterol, Venous Pressure, Vital Capacity and Clinical Course in Case 15, after Administration of 57 mc. of* I^{131}.

a period on a rice diet, digitoxin, supplementary vitamins and frequent injections of mercurial diuretics as well as thoracenteses, the patient improved only slightly during seven weeks of hospitalization.

Physical examination showed the patient to be dyspneic, orthopneic and slightly cyanotic. The blood pressure was 130/80. The neck veins were distended. There were dullness and diminished breath sounds at the right lung base posteriorly, with moist rales at both bases. The heart was enlarged to the anterior axillary line; the rhythm was grossly irregular. There was a Grade 1 apical systolic murmur. The abdomen was protuberant. The liver was firm, nontender and palpable 5 fingerbreadths below the right costal margin. The splenic tip was palpable. Pitting edema was ++ over the sacrum and + over the ankles.

Laboratory examination revealed a urine specific gravity of 1.019, with ++ to ++++ albumin; the sediment showed 1 to 10 white cells, occasional erythrocytes and fine granular casts. The blood was normal. The nonprotein nitrogen was 54 mg. per 100 cc. On x-ray examination, the heart was dilated to the left and the right. Electrocardiograms showed auricular fibrillation and evidence of old posterolateral infarction and left-ventricular hypertrophy.

On October 12 and October 23, 1948, the patient received 27 mc. and 30.5 mc. of I^{131}, respectively, and retained 39 mc. (Fig. 4). In the immediate post-treatment period, he continued to show 4- to 5-pillow orthopnea, dyspnea, markedly distended neck veins, auricular fibrillation with a pulse deficit of approximately 60, flatness and diminished breath sounds at the right base, enlargement of the liver to the level of the umbilicus, +++ edema of the left leg and + edema vital capacity is 3850 cc. (compared to 2200 cc. before treatment) and the arm-to-tongue circulation time is thirty seconds. The nonprotein nitrogen has remained at approximately 60 mg. per 100 cc.

DISCUSSION

For most patients with angina pectoris and congestive failure, medical treatment successfully alleviates discomfort and provides increased capacity for a satisfactory program of life. In some patients rapid progression of disease or complications such as acute myocardial infarction or embolic phenomena terminate life after a relatively brief intermediate period of severe discomfort or marked restriction of activity.

There is, however, a relatively small group of patients with angina pectoris or congestive failure who remain incapacitated and in great discomfort despite all available measures. The disease process may be relatively stationary for months or years, the patients enduring great discomfort from congestive failure or numerous daily attacks of angina pectoris, despite all medical measures. For these patients afflicted with severe angina pectoris, va-

rious surgical measures such as sympathectomy, posterior rhizotomy, omentopexy and pericoronary neurectomy have been employed. The fact that the work of the heart is lessened in myxedema and that alleviation of congestive failure and angina pectoris has long been witnessed in thyrotoxicosis when the metabolic rate is lowered from hyperthyroid to normal levels led to the employment of total thyroidectomy[7, 8] for the treatment of intractable heart disease. Parsons and Purks,[9] after making a survey of the literature and sending personal inquiries to all members of the leading surgical associations and to various American clinics, reported on the results of total thyroidectomy obtained in 362 patients. Of the 229 patients with congestive heart failure, 64 per cent showed excellent results, the remainder only slight or no improvement. A study of the 133 patients with angina pectoris revealed 56 per cent with excellent results, 28 per cent moderately improved and 16 per cent with only slight improvement or failure. The magnitude of the surgical procedure in such seriously ill patients (many with an inevitably short life expectancy), an over-all surgical mortality rate of 10 per cent in those with congestive failure and of approximately 5 per cent in those with angina pectoris, as well as the parathyroid and laryngeal complications, militated against the practicability of this method of treatment and prevented its widespread application. The frequency of worth-while improvement in these chronically crippled cardiac patients confirmed, however, the validity of the underlying rationale and indicated the desirability of inducing the hypometabolic state by medical rather than surgical means.

The striking effectiveness of the thiourea derivatives in alleviating thyrotoxicosis and reducing the metabolic rate to normal suggested their possible usefulness in producing hypometabolism or myxedema in euthyroid cardiac patients.[10-13] Unfortunately, however, hypothyroidism can be induced in certain patients only. The thiourea drugs are irregular in their action, producing various degrees of hypometabolism when they are effective. Favorable results in some euthyroid cardiac patients have been reported. To maintain the hypometabolic state in such persons, however, administration of the drug must be continued for the remainder of the patient's life. At any time during such administration dangerous drug reactions, including granulocytopenia, agranulocytosis and even death, may suddenly occur.[14-20]

The availability of I^{131} suggested its use for the purpose of inducing hypometabolism. The first problem was to learn whether persistent hypothyroidism could be induced safely by one or more doses of I^{131}. It is well known that thyrotoxicosis can be controlled by I^{131} with a reduction of the basal metabolic rate to normal. Three to 8 millicuries are commonly used. The avidity of the normal thyroid gland for I^{131} is much less, however; the uptake is usually 20 to 50 per cent of the administered dose, as indicated by urinary excretion, and averages 30 per cent as measured by external counting.[4, 5, 21] Before the therapeutic studies of the present communication were undertaken, observations were made with gradually increasing doses in euthyroid patients in terminal states due to hemiplegia or to other conditions such as carcinoma. The results of these studies indicated that persistent hypothyroidism could be induced by one or more appropriate doses without any toxic effects. Radiation sickness has not been observed in any patient. The studies of possible toxic effects throughout our investigation included examination of the blood and urine, uptake of radioiodine by organs other than the thyroid and histologic examinations.[22-24]

General Appraisal of Results

Each of the patients selected for treatment was in seemingly hopeless condition, having received all the usual medical measures and nevertheless remaining incapacitated for months or years. Although unexpected improvement in such patients occasionally occurs, the rather remarkable improvement observed in one third of all patients treated and the satisfactory improvement experienced by another third of the patients has been impressive. Some patients had been observed for years in the cardiac clinic of the Beth Israel Hospital and on the wards; others were referred by physicians who placed their records at our disposal. Each patient was evaluated independently by several of us before a decision was reached; in many instances our appraisal was based on observations and study of the patient, including objective tests such as exercise-tolerance and vital-capacity measurements over a period of weeks or many months before radioactive-iodine therapy was instituted. Some rejected patients failed to give sufficient objective confirmation of their incapacity when carefully studied; others were afflicted with associated diseases (such as bronchiectasis with advanced pulmonary emphysema, renal disease, cirrhosis of the liver, cerebral arteriosclerosis, active rheumatic fever or subacute bacterial endocarditis) that would render evaluation of the therapeutic result difficult. In others, the downhill course of the patient's condition made it seem probable that even if temporary improvement were induced the duration of life would nevertheless be short.

It was of considerable interest to observe the relation between clinical improvement and the occurrence of hypometabolism. The irregular interval of five weeks to six months after I^{131} treatment before hypothyroidism becomes evident is an additional safeguard against the possible effect of suggestion. The time at which hypometabolism and clinical improvement occur cannot be foretold by

the patient or the physician; the clinical improvement, first noted by the patient and later found to be coincident with the inception of hypometabolism when the results of the serum-cholesterol and basal-metabolic determinations are made available, is consequently the more impressive. Conversely, some patients showed thyroiditis one to two weeks after I^{131} therapy, with pain, tenderness and increased heat over the thyroid area, and noted that their condition was definitely worse. In some of these patients the basal metabolic rate was slightly elevated and the serum protein-bound iodine increased. As clinical improvement became evident, the degree of improvement was generally proportional to the degree of hypothyroidism. This correspondence between metabolic levels and clinical cardiac status was observed on 31 occasions in the first 23 patients treated.

Selection of Cases

Although it is too early to formulate final indications and contraindications, it is nevertheless desirable to offer a tentative opinion concerning the criteria for proper selection based on our experience in these 23 patients observed in the hypometabolic state for seven to twenty-six months.

Unfavorable factors that incline us to advise against treatment may be summarized as follows:

Rapidly progressive cardiovascular disease (malignant hypertension, syphilitic cardiovascular disease). There is no reason to believe that hypothyroidism retards the progression of the underlying pathologic process. The radioactive-iodine treatment of heart disease is not to be considered as curative; it is a palliative procedure that is to be regarded as an adjunct to the recognized medical measures. Even though the patient may experience improvement for a few weeks or months after treatment, a relapse to his former clinical condition is likely to occur if a rapidly advancing pathologic process underlies his difficulties. It is also unwise to treat patients who are in the terminal phases of their disease, particularly since five weeks to six months intervene before the hypometabolic state is attained. However, the presence of moderate or even marked hypertension does not contraindicate the treatment.

Low basal metabolism. The presence of preexisting low basal-metabolic rates is a contraindication to treatment. Patients with a basal metabolic rate of −15 per cent or lower, although relieved of their symptoms when myxedematous at −35 or −40 per cent, suffer a recurrence of their symptoms when maintained at the necessary level of −20 to −25 per cent, which is only slightly below their pretreatment level (Case 10).

Associated conditions. The presence of other conditions that may incapacitate the patient and becloud evaluation of this method of treatment constitutes a contraindication. These include active infection such as rheumatic fever (Case 17), bronchiectasis, emotional instability (Cases 12 and 13), cirrhosis of the liver and recent acute myocardial infarction. Intermittent claudication (Case 11) is not benefited by the induction of hypometabolism; on the contrary, it may be aggravated and constitutes an unfavorable factor.[3]

Favorable factors. The patients who may be expected to gain the greatest benefits are those in whom the disease has been relatively stationary or only slightly progressive over a period of one or more years[3] (Cases 1-6). Even though such patients may be seriously incapacitated and may have angina pectoris at rest in bed, if their condition is stabilized over a period of three months or more a favorable response to this treatment is likely. Patients with congestive failure should show evidence of some cardiac reserve, such as ability to lose the signs of congestive failure on bed rest or with the use of diuretics and digitalis[3] (Cases 14–16). The basal metabolic rate should be above −10 per cent. It is important that the patient be alert, co-operative and emotionally stable. It has been our experience that hyperactive, tense patients are particularly favorable candidates.

When patients are frankly myxedematous, with basal metabolic rates of −30 to −40 per cent, they are often irritable and nervous, but on receiving small doses of thyroid to maintain them at a level of −15 to −25 per cent they are frequently more placid and even-tempered than before treatment, though mentally as acute as formerly. In an occasional patient, such as J. K. (Case 3), this factor may be significant, the patient stating that all his life prior to treatment he was prone "to fly off the handle, whereas now I am more even-tempered." The precise mechanisms responsible for the beneficial effects in these high-strung patients is not clear. The adrenal and other endocrine organs may well be involved.[3]

Program of I^{131} Treatment

Our present program of treatment entails the following measurements and observations: In every instance tracer doses of 100 to 150 microcuries of I^{131} are administered. The uptake of I^{131} by the thyroid is measured by the direct counting technic previously described.[4, 5] This measurement is made twenty-four hours, forty-eight hours, seventy-two hours and ninety-six hours after the administration of I^{131} by mouth. From these data the biologic half-life is estimated and the equivalent dosage in roentgens delivered to the thyroid is calculated.[21] As a check on this, the urinary excretion of I^{131} is also measured[22, 23] for each of the three days following the administration of I^{131} by mouth. Assuming that the normal thyroid weighs 25 to 30 gm., the initial dose is calculated to deliver approximately 30,000 to 50,000 equivalent roentgens. Since the average euthyroid twenty-four-hour uptake is

approximately 30 per cent and is turned over with an average biologic half-life of 7 days, the initial dose of I^{131} is approximately 30 mc.[25]

After the administration of the therapeutic dose, similar measurements are made by direct counting of the uptake of the dose by the thyroid twenty-four, forty-eight and seventy-two hours after its administration to ascertain the amount of the therapeutic dose retained in the thyroid.

During the next few weeks the patient is observed closely. During this period and later, we have made numerous observations of possible toxic effects and of the occurrence or absence of thyroiditis. We have observed the ambulatory patients three times weekly for two weeks. It is, of course, imperative to instruct all patients concerning the safety precautions relative to contamination of clothing and skin, storage of urine immediately after the therapeutic dose and other necessary safeguards. Approximately two thirds of the patients have exhibited mild to moderate thyroiditis lasting one to ten days. It has been severe in only one instance. No treatment except the use of analgesics has been indicated. Inasmuch as thyroid hormone is apparently released during the stage of thyroiditis, the activities of the patient should be reduced to a minimum during this time.

After the first two weeks the patient is seen by us at one- to two-week intervals, at which time serum-cholesterol, basal-metabolic-rate and other measurements are made, in addition to a clinical appraisal of his condition. Careful inquiry in regard to early signs of hypometabolism is made. In our experience hypometabolism has developed five weeks to six months after an adequate dose* of I^{131}. When patients do not develop hypometabolism within several months, it has been our practice to administer additional doses after preliminary tracer-dose studies to determine whether residual tissue capable of taking up I^{131} exists (Cases 1, 2, 19, 21, 23, 24 and 27). The average number of doses per patient was 2.3, but more than 3 doses of I^{131} were necessary for 6 patients. As many as 4, 5 or even 6 doses at various periods of time have proved to be necessary, but in each case myxedema was finally achieved (Table 1).

Repeated administration of I^{131} is particularly indicated when thyroid adenomas are present (Cases 8, 19 and 23). In some patients these adenomas are plainly evident at the time of initial examination. In other patients they have become apparent only after the normal thyroid has disappeared after the first one or two doses of I^{131}. Presumably these nodules are initially nonfunctioning and do not take up I^{131} until the normal thyroid tissue has been destroyed. The adenomas apparently then begin to function and may be affected by subsequent doses of I^{131}. Subsequent doses frequently lead to tenderness and gradual disappearance of the nodule, the induction of myxedema with its characteristic clinical manifestations, rise in serum cholesterol and lowering of the basal metabolic rate.

The first clinical intimations of incipient hypothyroidism may consist of one or more of the following: slight fullness or puffiness of the face, increased sensitivity to cold, slight stiffness of the joints or arthralgia and paresthesias. Concomitantly, the patients usually report that the attacks of angina are milder or less frequent or that dyspnea and orthopnea are diminished. It has been our practice to permit marked hypothyroidism or, in some instances, even complete myxedema to develop, in order to assure ourselves that all thyroid tissue has been affected, and then to give 6 or 12 mg. of thyroid daily. In each patient thyroid dosage must be adjusted to maintain him at the lowest metabolic level at which he experiences the maximum relief from his cardiac disease and the minimum discomfort from myxedema. In certain cases this may not be possible, the patient showing little or no improvement over his pretreatment status when sufficient thyroid is administered to obviate the discomfort. Most patients are maintained at a level of approximately −20 to −25 per cent on a daily dosage of 6 to 30 mg. of thyroid.

Occasionally patients may suffer a recurrence of their symptoms because residual thyroid tissue has regenerated with return of the metabolic rate to pretreatment levels. In such instances, thyroid is withdrawn, and after tracer doses show adequate uptake of I^{131} an additional therapeutic dose is administered.

In addition to these special considerations, the same careful supervision and therapeutic program indicated for all patients with heart disease is essential.

TABLE 1. *Dosage in 37 Euthyroid Patients with Chronic Heart Disease.*

No. of Doses	No. of Patients
1	9
2	18
3	4
4	2
5	3
6	1

*Total Dose — Range ..... 25.5–200.0 mc.
Average ..... 64.5 mc.
Largest Single Dose ..... 51.0 mc.
Average Total Body Retention (30 Cases) ..... 20.5 mc.

Hypercholesterolemia, Myxedema and Arteriosclerosis

The question naturally arises whether the high cholesterol values and myxedema dispose the patient to an increased progression of arteriosclerosis. In our own patients, the situation is not strictly analogous to untreated complete myxedema, since our patients receive small doses of thyroid. In this connection we have reviewed the clinical course and post-mortem findings of patients who survived one to eleven years after surgical total thyroidectomy

and in whom hypometabolism with elevated cholesterol values was present.

We have been particularly interested in the younger patients with rheumatic heart disease. In them, only slight or minimal conorary arteriosclerosis would ordinarily be anticipated at death. If decided arteriosclerotic lesions were observed post mortem in such patients, the lesions might well be attributed to the myxedematous state. In all 5 such patients who survived one to eleven years in the hypothyroid state after surgical total thyroidectomy, careful post-mortem studies by the Schlesinger technic have revealed only minimal or no coronary arteriosclerosis. Although the number of patients is small, these results demonstrate that progressive arteriosclerosis of the coronary arteries is not a necessary concomitant of the hypercholesterolemia of hypothyroidism.

The Question of the "Myxedema Heart"

As in previous studies, particular attention has been devoted to the appearance of the signs or symptoms of the so-called "myxedema heart."

An increased cardiac silhouette or area of percussion dullness, decreased voltage of the electrocardiogram and less forceful pulsations on fluoroscopy have been observed in some of our subjects. "Myxedema heart," however, in the sense of a condition aggravating or precipitating attacks of angina pectoris or congestive failure, did not develop in our cardiac patients. On the contrary, with the appearance of such changes, striking clinical improvement has been witnessed. In some patients with congestive failure the cardiac silhouette became smaller, the disappearance of the dilation of the failing heart offsetting the effect of myxedema on the heart. Our experience is consequently in accordance with that of Willius and Haines,[26] Means, White and Krantz[27] and Christian,[28] who concluded that "myxedema heart" in the sense of heart failure occurs rarely if at all.

Summary and Conclusions

The results of hypometabolism induced by I^{131} in patients incapacitated by angina pectoris or congestive failure have been reported. Of the 37 euthyroid cardiac patients treated to date, 23 patients have been followed in the hypometabolic state for seven to twenty-six months, with an average of one-and-a-half years.

Hypothyroidism can be regularly induced in euthyroid patients by one or more appropriate doses of radioactive iodine, I^{131}.

No serious toxic or untoward reactions have occurred. Transitory mild hyperthyroidism in two patients and thyroiditis in approximately two thirds of the patients have been observed.

In general, one third of the patients have shown rather remarkable improvement; in another third the improvement has been definitely worth while; in another third no worth-while improvement was achieved.

In the clinical management of these patients we have attempted to maintain the lowest metabolic rate consistent with the comfort of the patient and have administered small doses of thyroid after the induction of myxedema.

This group represents the intractable cardiac cripples who are ordinarily considered for surgery. Hypothyroidism induced by radioactive iodine promises to accomplish worth-while improvement through medical means without the inevitable risk and complications of surgical intervention.

Final evaluation of this therapy must await prolonged study. At present it can be said that many months of worth-while existence have already been added to the lives of disabled cardiac patients who were refractory to all standard forms of medical therapy.

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AUREOMYCIN IN THE TREATMENT OF ACTINOMYCOSIS*

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ALTHOUGH actinomycosis has been described for over 70 years, its frequency and potential seriousness have not been given recognition in the American literature until quite recently. The first monograph in English on this subject was not published until 1938.[1] Since then, numerous articles dealing with this condition have appeared. With an increased awareness on the part of physicians and dentists, together with steadily improving diagnostic facilities, an increasing recognition of this infection is to be expected. Although much progress has been made in the treatment of actinomycosis, the mortality and morbidity are still significant. This is especially true in the thoracic, abdominal, neurologic and systemic forms of the disease. Recently we reported the successful treatment of a case of cervicofacial actinomycosis with aureomycin.[2] This paper consists of a report of 2 additional cases of cervicofacial actinomycosis and 1 case of actinomycotic hepatic abscess successfully treated with aureomycin. In-vitro studies are also reported.

Actinomycosis is the name applied to the condition resulting from invasion and growth in the body tissues of a micro-organism, the actinomyces. In 1877 Bollinger[3] described actinomycosis in animals, and Harz[4] designated the causative organisms as actinomyces and the disease as actinomycosis. Ponfick,[5] in 1879, established the causative role of actinomyces in the human disease. In 1885, Israel[6] published the first adequate clinical account of actinomycosis.

In 1890, Bostroem[7] began a controversy that has only recently been resolved. He asserted that actinomycosis was most likely caused by an aerobic organism that had its natural habitat in grain. Israel,[8] Wolff[8] and Wright[9] disagreed, insisting that the causative agent was anaerobic, required body temperature and could not exist out of the body. It is now recognized that the actinomycetes constitute a large group of organisms that are to be found constantly in dust and soil and on grass, grain, hay and decaying vegetable matter. They are aerobic and anaerobic. They range from the strictly parasitic, obligatory anaerobic actinomyces proper, which are bacteria-like in their chief characteristics, to the mold-like Streptomycetaceae. According to Conant and Rosebury,[10] the only members of the group of medical importance are the anaerobic *Actinomyces bovis*, the causative agent of actinomycosis in man and in animals, and several aerobic species of Nocardia that cause nocardiosis in man and in animals.

The pathogenic actinomyces have never been found in nature apart from a parasitic habitat. In 1925, Naeslund[11] isolated *Actinomyces bovis* from the normal human mouth. Since then, these organisms have been obtained in the absence of disease from the crypts of tonsils, tartar on teeth, pyorrhea pus, carious teeth, salivary calculi and the gums of man. It is believed, therefore, that actinomycotic infections are endogenous in origin. Although usually saprophytic, under proper conditions they may gain access from the intestinal tract, — especially the mouth, — and become pathogenic. The following traumatic events have been associated with subsequent actinomycosis: tooth extraction or other injury to the mouth or throat; human bite or knuckle injuries from a blow to the teeth; aspiration of an extracted carious tooth; and tonsillectomy. Transmission of this infection from man to man or from animal to man has never been established. It has been demonstrated that the incidence of actinomycosis is no greater in rural than in urban areas.

Actinomycotic infection leads to the formation of a granulomatous lesion, with overproduction of fibrous and connective tissue. Suppuration is usually limited in degree; multiple interconnected abscesses form that rupture to the surface, forming multiple draining sinuses. *Actinomyces bovis* are demonstrable microscopically or culturally in the pus or lesion. Sulfur-like granules may be present. The organisms may be widely spread

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through the bloodstream; the lymphatic system is rarely involved. Bone may be eroded but is seldom affected interstitially except in the jaw.

Fifty-eight cases of actinomycosis had been reported in the United States in 1899; 100 in 1902; and about 700 in 1922.[11] Since then, each year has seen an increasing number of cases recorded.

In 1938, Cope[1] reviewed 1330 cases of actinomycosis and found the following incidence: cervicofacial, 56.7 per cent; abdominal, 22.3 per cent; thoracic 14.9 per cent; other parts 5.1 per cent. Although involvement of the skin secondary to lesions of underlying organs is not rare, it is doubtful if the primary site of actinomycosis is ever in the skin.[10]

Itterson and Netter,[12] in 1885, introduced potassium iodide for the treatment of human actinomycosis. Since that period, innumerable therapeutic agents have been utilized, including vaccines, copper sulfate, thymol, radiation (x-ray irradiation and radium emanations), surgical drainage and excision, sulfonamides,[14] penicillin[15] and diasone[16] (disodium formaldehyde sulfoxylate).

The cervicofacial type of actinomycosis represents more than half the human cases. Three of the 4 cases included in this series fall into this category. It is noteworthy that all 3 infections in this group followed the extraction of teeth. In the face of a subacute or chronic inflammatory process in the cervicofacial region, the diagnosis of actinomycosis should be considered, and the purulent material should be examined grossly for sulfur granules as well as microscopically and culturally for *Actinomyces bovis*. Although the prognosis in cervicofacial and localized cutaneous lesions is best, it should be remembered, as was pointed out by Davis[12] in 1941, that generalized metastases may result. There are numerous recent reports of cervicofacial actinomycosis successfully treated by the prolonged administration of penicillin.[14, 15, 17]

Pulmonary actinomycosis, which constitutes approximately 15 per cent of cases, still represents a therapeutic problem. This type of infection probably results from the aspiration of infected material from the mouth. A pneumonic process results, with suppuration and fibrosis. The pleura is usually involved, and frequently multiple thoracic sinuses result. One or both lungs may be involved. Kay[18] reported 2 cases treated with intensive courses of sulfadiazine and penicillin alone and in combination almost continuously for one year without effective results. Pneumonectomy was finally required in both cases. There have been, however, several reports of the successful treatment of pulmonary actinomycosis with penicillin.[19, 20]

Until the appearance of the sulfonamides and penicillin, the prognosis for abdominal actinomycosis, which accounts for about 20 per cent of cases, was grave. This type of infection, according to Farris and Douglas,[21] usually results from a diseased appendix. Wangensteen,[22] in 1936, reported 5 cases of abdominal actinomycosis. Four of the patients had died; the fifth showed improvement. Kolouch and Peltier[23] reviewed 330 cases of abdominal actinomycosis and reported 30 per cent cured, 10 per cent improved, 54 per cent dead and 6 per cent not followed. In this investigation 16 patients were treated with sulfonamides, with 56 per cent cured, 18 per cent improved, 18 per cent dead and 4 per cent not followed. Sanford and Barnes,[24] in 1949, reviewed the literature and found reports of 19 patients with abdominal actinomycosis who were treated with penicillin. In this group, the mortality rate was 15.8 per cent. These authors reported 2 cases of abdominal actinomycosis that did not respond to the following therapy over a period of eight to nine months: penicillin in large doses (800,000 units daily), sulfonamides, adequate surgery and supportive therapy. However, the use of penicillin in massive doses was successful. One patient was apparently cured in sixty-seven days after an illness of sixteen months. In this particular case, the patient, who had already received 128,525,000 units of penicillin and 874 gm. of sulfadiazine, was given 644,480,000 units of penicillin and 156 gm. of sulfadiazine in sixty-seven days. The second patient, who had already received 58,720,000 units of penicillin and approximately 1000 gm. of sulfadiazine, was given 586,400,000 units of penicillin in forty-eight days. Sanford and Barnes[24] conclude that the massive use of penicillin, in conjunction with adequate surgery and supportive therapy, constitutes the most promising therapeutic regimen.

In view of these facts, it was evident that an improved method of treatment of actinomycosis was needed. Therefore, we decided to investigate the effectiveness of aureomycin in this condition. The successful treatment of 1 case of cervicofacial actinomycosis with aureomycin was reported previously.[2] Since that time, 2 additional cases of cervicofacial and 1 case of abdominal actinomycosis have been treated.

Case Reports

Case 1. E. T., a 24-year-old man, was admitted on March 6, 1950. A left lower molar tooth had been extracted on August 14, 1949. Three weeks later, painless external swelling was noted over the left lower jaw. A physician was consulted; he administered 300,000 units of penicillin intramuscularly and placed the patient on 1 gm. of sulfadiazine every six hours for seven days. However, by the last week of September trismus was so marked that the patient could take only liquids. Shortly thereafter the lesion ruptured spontaneously; pain and trismus subsided enough that the patient was able to resume a regular diet. One week later swelling was again noted. Essentially painless induration persisted until January 3, 1950. On that date the lesion was incised externally and internally by a physician. In addition, the patient was given 300,000 units of penicillin intramuscularly every twenty-four hours for ten days. Temporary amelioration of symptoms resulted, but between this period and March 6 spontaneous rupture occurred 6 times.

Examination revealed that the temperature was 99.4°F, the pulse 92, the respirations 18 and the blood pressure 132/84.

A large mass measuring 5 by 5 cm. was observed overlying the lateral aspect of the angle of the left mandible (Fig.

1*A*, 1*B*). Palpation revealed moderate tenderness, the mass being woody in consistency except for a small central fluctuant zone. Intraoral examination revealed no communication, although induration was felt with the use of a tongue blade. The site of the previously extracted left lower molar tooth could be observed. It was impossible for the patient to separate the anterior teeth by more than 1 cm. Roentgenograms of both mandibles revealed no bony involvement.

Immediately after hospitalization the fluctuant area was incised; 2 cc. of yellowish purulent material was obtained. Two sinus tracts were located. One extended 0.5 cm. medially and superiorly; the second was of similar length but extended medially and inferiorly. A moist preparation disclosed the typical sulfur-like granules of *Actinomyces bovis*. This diagnosis was subsequently confirmed microscopically and by culture.

After incision of the lesion, the patient was able to separate the jaws by 2 cm. The sinuses were irrigated with 100 mg. of aureomycin in normal saline solution and oral aureomycin was begun, 750 mg. every 6 hours. Twenty-four hours later the patient was able to separate the teeth by 3 cm., could eat a regular diet and noted no pain. For the ensuing three days the sinuses were irrigated every twenty-four hours with 100 mg. of aureomycin in saline solution. Forty-eight hours after the institution of aureomycin therapy, all drainage had ceased and the mouth could be opened 3.5 cm. On the sixth hospital day the teeth could be separated anteriorly 4 cm., although some limitation of motion of the left jaw was still present. By the tenth day, full range of motion of the jaws had returned and the indurated lesion had decreased in size to 2.5 by 2.0 cm.

On the eleventh hospital day, aureomycin was reduced to 2 gm. daily, with 500 mg. being administered 4 times a day between meals and at bedtime. Also on that date the patient was discharged from the hospital, to be observed through the Out-Patient Department. This permitted the patient to resume his work. Aureomycin was discontinued after a total of twenty-eight days of administration. Throughout treatment, supplementary vitamins were administered. No toxic reactions to aureomycin were noted. The total amount of this antibiotic used was 66 gm. Initially the patient was examined at weekly intervals after his discharge from the hospital: thereafter he returned to the clinic each month. There was a progressive diminution of induration, until four months after the completion of treatment only minimal induration could be palpated (Fig. 1*C*, 1*D*). The patient was entirely asymptomatic and had gained 5 to 6 pounds since treatment was discontinued.

Laboratory examination revealed a white-cell count of 16,200, with 79 per cent polymorphonuclear leukocytes, 20 per cent lymphocytes and 1 per cent eosinophils, and a red-cell count of 4,240,000, with a hemoglobin of 13.5 gm.; a urinalysis was within normal limits.

FIGURE 1. *Photographs of Patient in Case 1.*
A and B= at the start of aureomycin therapy; C and D= four months after treatment.

CASE 2. F. B., a 39-year-old man, was seen in the General Medicine Clinic on March 27, 1950, having been referred by the Dental Surgical Service. On December 12, 1949, a lower molar had been extracted. Ten days later swelling was noted over the external aspect of this region. This rapidly progressed to the formation of a painful, tender, erythematous mass that was about the size of a small orange. Temporary relief followed the use of 300,000 units of penicillin, injected intramuscularly every twenty-four hours for six days. The lesion did not drain spontaneously and was not incised. During the ensuing two-and-a-half months intermittent painless swelling was noted on 6 occasions.

Finally, on March 9, the patient was hospitalized on the Dental Surgery Service. At that time examination revealed a temperature of 99°F., with the pulse 88, the respirations 16 and the blood pressure 126/76. An indurated, slightly erythematous mass measuring 7 by 5 cm. was observed overlying the lower margin of the right mandible and extending downward over the right aspect of the neck. One small area was fluctuant on palpation. The adjacent cer-

vical lymph nodes were moderately enlarged but not tender. A roentgenogram of the mandibles disclosed an area of minimal bone destruction at the original site of the third right molar. After hospitalization of the patient the fluctuant area of the lesion was incised, yielding a small amount of purulent material, which on culture revealed nonhemolytic *Staphylococcus aureus*. A therapeutic regimen was begun that consisted of 100,000 units of penicillin given intramuscularly on admission followed by administration of 50,000 units every three hours for three days. Intermittent hot saline soaks were applied locally to the lesion. Since clinical response was poor, sulfadiazine therapy was begun, using 3 gm. initially and later 1 gm. every four hours. Since there had been some reduction in the size of the lesion, the March 27: 750 mg. of aureomycin 4 times a day (between meals and at bedtime) for ten days, after which the dosage was reduced to 2 gm. daily, 500 mg. being given at the same time intervals. Medication was discontinued after twenty-eight days. There was rapid initial improvement, the drainage disappearing after ninety-six hours. Three months after the conclusion of treatment only minimal induration could be palpated, and the patient was entirely asymptomatic (Figure 2*C*).

In-vitro sensitivity studies with the actinomyces isolated from this patient using aureomycin revealed a definite inhibitory action.

The only toxic reactions to aureomycin were intermittent transient vertigo of slight degree and mild nausea, which was

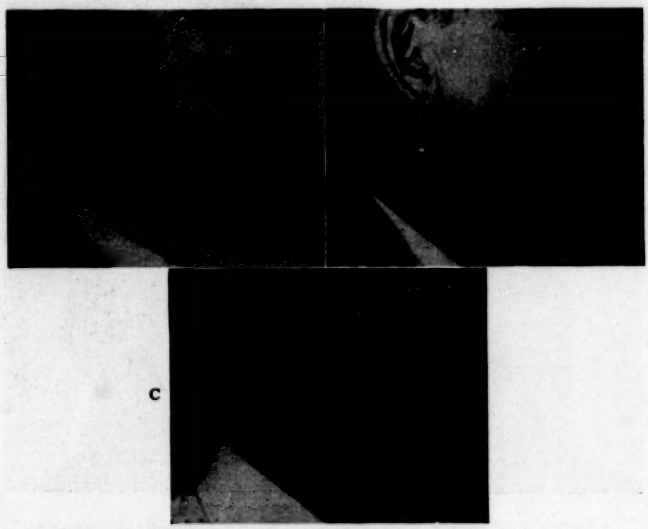

FIGURE 2. *Photographs of Patient in Case 2.*
A = at the start of aureomycin therapy; B = at the conclusion of therapy; C = three months after the completion of treatment.

patient was discharged to the Out-Patient Department on March 13, 1950. On the following day a positive culture for *Actinomyces bovis* was obtained, and the patient was instructed to report to the General Medicine Clinic for evaluation.

Examination on March 24, 1950 (11 days after discharge), revealed a large mass (Fig. 2*A*) measuring 6 by 3 cm. involving the lower border of the right mandible and extending downward onto the neck. The lesion was slightly tender and seemed woody on palpation. A slight amount of yellowish purulent material was draining from the site of the previous surgical incision. Microscopical and cultural studies established the diagnosis of actinomycosis. A moderate degree of trismus was present; the teeth could be separated anteriorly only by 2½ cm. Sulfur-like granules were again noted on March 27, and another culture obtained on that date was positive for *Actinomyces bovis*.

It was decided to treat this patient entirely on an ambulatory basis. He was instructed to report to the Medical Clinic at weekly intervals for 4 visits and to return once each month thereafter. The following regimen was begun on relieved by giving 100 cc. of milk and a few crackers immediately after medication. Throughout treatment the patient did not lose a single day from his work. The total dose of aureomycin employed in this case was 66 gm. Supplementary vitamins were not administered.

CASE 3. S. L. F., a 47-year-old man, was hospitalized on April 10, 1950. Two years previously he had noted the onset of gastrointestinal symptoms consisting of intermittent colicky right-upper-abdominal pain of a gnawing character. This pain was more severe when the stomach was empty. Relief was obtained to some degree by eating or by purging. He had noted associated flatulence and belching. A small abdominal mass had been observed at that time. All these symptoms gradually receded but recurred rather abruptly two months prior to hospitalization. Associated with the recurrence of these symptoms was the reappearance and subsequent rapid growth of an abdominal mass. Flatulence and constipation became progressively marked. The abdominal pain was no longer relieved by food or by purging and was now constant. Four weeks prior to hospitalization

tarry stools were observed. Dyspnea on exertion had been noted for several weeks; pedal edema, for one week. During the month before admission the patient had lost 10 to 20 pounds, and weakness had become progressively severe. Constant bed rest had been required for one to two weeks. He had had no nausea or vomiting. A low-grade elevation of temperature had been noted for several weeks.

Examination showed the temperature to be 98° F., the pulse 80, the respirations 24 and the blood pressure 130/76. The conjunctivas were pale. There was slight cardiac enlargement. A mass measuring 12 to 15 cm. in diameter was located in the midline of the upper abdomen, extending inferiorly to the umbilicus. This mass moved slightly with respiration, appeared to be fixed and was tender on palpation. It appeared to be continuous with the liver, which could be palpated 4 cm. below the right costal margin. The left lateral border of the mass was fluctuant. Abdominal ascites was present.

For twelve days after admission the patient was studied by various laboratory and roentgenologic technics. During this period the patient displayed a spiking type of temperature elevation that reached at least 102° F. daily. The admission laboratory studies revealed a red-cell count of 3,940,000, a hemoglobin of 9 gm., a hematocrit of 26.5 per cent and a white-cell count of 5150, with 63 per cent polymorphonuclear leukocytes, 33 per cent lymphocytes, 3 per cent monocytes and 1 per cent basophils. A urinalysis was within normal limits; stool examination revealed ++++ occult blood. The total plasma protein was 6.6 gm. per 100 cc., the albumin 2.1 and the globulin 4.5 gm.; the cephalin-flocculation, serum-bilirubin, prothrombin-time and bromsulfalein determinations were within normal limits. Blood cultures were negative. An abdominal paracentesis yielded approximately 1000 cc. of straw-colored fluid that had a specific gravity of 1.026 and a cell count of 250 per cu. mm., with 50 per cent lymphocytes and 50 per cent red blood cells. Gram-stained and acid-fast preparations were negative, as were cytologic studies for tumor cells. An upper-gastrointestinal roentgenologic series revealed displacement of the stomach to the left and posteriorly by a large, extra-alimentary soft-tissue mass that appeared to be the left lobe of the liver. A barium-enema examination showed displacement of the transverse colon slightly downward. Chest roentgenograms disclosed cardiac enlargement, with the contour suggesting left-ventricular preponderance. There was slight elevation of the left leaf of the diaphragm.

Eight days after admission the fluctuant area in the left lobe of the liver was aspirated; 160 cc. of thick yellowish-green, fecal-smelling material was obtained. Sulfur-like granules were present on examination, and culture established the presence of *Actinomyces bovis* and *Bacteroides fundulifórmis*. Cytologic study disclosed only necrotic liver tissue and cellular debris.

On the twelfth hospital day, parenteral administration of aureomycin was begun, using 1 gm. in 1000 cc. of a 5 per cent solution of glucose intravenously every eight hours. Alternate preparations were given intravenously in normal saline solution and distilled water. Simultaneously, 750 mg. of aureomycin was given orally every four hours. Supportive therapy consisted of a high-protein and low-sodium diet, repeated whole-blood transfusions, 0.3 gm. of ferrous sulfate 3 times a day, a vitamin cocktail 3 times a day, 10 cc. of a 95 per cent solution of alcohol 3 times a day before meals and 1 cc. of crude liver injected intramuscularly every other day. One week after the institution of aureomycin therapy, intravenous medication was discontinued, as the spiking elevation had been replaced by a low-grade temperature. However, the orally administered aureomycin was increased to 1 gm. every four hours. At this point the patient developed cardiac decompensation. This complication was controlled by digitalization and mercurial diuretics.

At the time of the institution of aureomycin therapy, the abdominal mass had enlarged to the extent that the overlying skin was taut and shiny. The surgical consultants believed that immediate surgical drainage was necessary. However, it was decided to use frequent aspirations. The abscess was therefore aspirated 3 times, at twenty-four-hour intervals, yielding respectively 400 cc., 150 cc. and 10 cc. of material; 3 times at forty-eight-hour intervals, yielding 300 cc., 100 cc. and 50 cc.; and 3 times thereafter at ninety-six-hour intervals, yielding 35 cc., 20 cc. and 12 cc. After each aspiration 500 mg. of aureomycin in 50 cc. of normal saline solution was instilled into the cavity. Eight days after the institution of aureomycin, the aspirated material became thin and odorless. At that time, also, it became negative for Bacteroides on culture but remained positive for *Actinomyces bovis* for an additional four days. After fourteen days of therapy, an anterior-abdominal-wall abscess developed over the involved hepatic area, and a short needle was adequate for aspiration. At no time, however, did sinus formation occur. The patient remained afebrile after the nineteenth day of treatment and slowly gained strength and weight. On the twenty-third day of therapy, aureomycin was reduced to 500 mg. every six hours; this was continued until discharge from the hospital thirty-five days later. The total period of hospitalization was seventy days.

After discharge the patient was observed at weekly intervals in the Medical Clinic. It was necessary to continue administration of 0.1 gm. of digitalis daily. In addition, 1 gm. of ammonium chloride was given 3 times a day. On this regimen there was no evidence of cardiac decompensation. Eleven weeks after the completion of therapy the only abdominal finding was minimal superficial induration about the sites of repeated aspiration. No tenderness was present. The patient's weight, which had been 110 pounds during his hospital stay, had increased to 152 pounds. His average normal weight was said to range from 150 to 155 pounds. It is noteworthy that reversal of the albumin-globulin ratio of the plasma protein persisted until one month after release from the hospital. A flat plate of the abdomen taken one month after discharge was entirely normal. There were no significant toxic reactions to aureomycin. The total dose of aureomycin employed in this case consisted of 21 gm. intravenously and 158 gm. orally.

Laboratory findings (during hospitalization and a two-month observation period) showed that the hematocrit ranged from 20 to 39 per cent and the white-cell count from 12,800 to 5150, with polymorphonuclear leukocytes from 80 to 53 per cent, lymphocytes from 15 to 44 per cent, monocytes from 2 to 4 per cent, basophils from 0 to 2 per cent and eosinophils from 0 to 1 per cent. Repeated urinalyses were within normal limits. Fecal occult blood ranged from ++++ to +; the bromsulfalein retention from 5 to 6 per cent (normal, less than 5); the prothrombin times from 44 to 100 per cent of normal; and cephalin-flocculation determinations at twenty-four hours from ++ to 0 and at forty-eight hours from +++ to 0. The total serum bilirubin varied from 1.2 to 0.5 mg. per cc.; the total plasma protein from 6.6 to 9.0 gm. per 100 cc., with albumin from 2.1 to 3.9 gm. and globulin from 6.4 to 3.4 gm.; the nonprotein nitrogen from 61 to 37 mg. per 100 cc.; and the serum cholesterol from 80 to 185 mg. per 100 cc. Twenty-four-hour urine-urobilinogen determinations ranged from 0 to 4.4 Ehrlich units. The blood serology was negative. The sedimentation-rate maximum fall per minute (Wintrobe, corrected) varied from 1.2 to 0.4 mm.; seven blood cultures were negative; 3 cultures of the material aspirated from the hepatic abscess were positive for both. *Bact. fundulifórmis* and *Actinomyces bovis*. Two later cultures were positive for only *Actinomyces bovis*; subsequently 4 were negative; 9 stool specimens were negative for *E. histolytica*; 6 cultures of aspirated hepatic material were negative for *E. histolytica;* and culture of ascitic fluid was positive for hemolytic *Staph. aureus*. Aureomycin blood levels varied from 32 to 2 microgm. per cc.; repeated aureomycin levels on aspirated hepatic material immediately prior to instillation of aureomycin were 0.5 microgm. per cc. In-vitro sensitivity studies with isolated *Bact. fundulifórmis* and *Actinomyces bovis* organisms revealed that the Bacteroides organisms were inhibited by 0.19 microgm. per cc. of aureomycin but were not inhibited by 50 microgm. per cc. of penicillin, streptomycin, chloramphenicol, neomycin or actidione. The *Actinomyces bovis* were inhibited by 0.78 microgm. per cc. of penicillin but were not inhibited by 50 microgm. per cc. of streptomycin, aureomycin, chloramphenicol, actidione or neomycin.

Discussion

Actinomycotic infections in man are being recognized with increasing frequency. Improved and more easily available bacteriologic facilities, to-

gether with closer co-operation between the various medical and dental specialties, should lead to steadily increasing appreciation of the significance of this infection. The possibility of actinomycosis should be considered in the diagnosis of all subacute and chronic inflammatory processes, especially in those involving the cervicofacial region.

The therapy of actinomycosis still presents a challenge. Numerous agents have been employed in the treatment of this infection. However, it was only after the advent of the sulfonamides and penicillin that the prognosis was materially improved. Even with the prolonged and combined use of these agents and appropriate surgical procedures, the morbidity and mortality of actinomycosis has remained significantly high. This is especially true in the thoracic and abdominal forms of the disease.

The successful treatment of 3 cases of cervicofacial and 1 case of abdominal actinomycosis with aureomycin is, therefore, of importance. Noteworthy is the fact that no major surgical procedure was required. The treatment of cervicofacial actinomycosis on an ambulatory basis with no interruption of employment is of great practical value. Likewise, oral medication is much to be preferred to the intramuscular route required for penicillin therapy. This is especially true when treatment must be prolonged, as is the case in actinomycosis. In no instance were significant toxic reactions to aureomycin noted.

In-vitro sensitivity studies on *Actinomyces bovis* isolated from 2 of these patients and from 2 additional cases not included in this series established a definite inhibitory action by aureomycin. Aureomycin exerts a bacteriostatic effect on *Actinomyces bovis*, although certain strains are evidently more resistant to aureomycin than others. This variation in sensitivity was previously noted with penicillin,[25] and it was suggested that concomitant secondary infection might play a part in this phenomenon.[11, 12, 25]

Although the post-therapeutic observation periods in these 4 cases are relatively brief (eight, five, four, and two-and-a-half months), the uniformly excellent response is most encouraging. In view of the rapid clinical response, ease of administration and lack of significant toxic effects, aureomycin appears to be the agent of choice in the treatment of actinomycosis.

Summary

Three cases of cervicofacial and 1 case of abdominal actinomycosis were successfully treated with aureomycin.

In-vitro sensitivity studies established a definite inhibitory action by aureomycin on *Actinomyces bovis*.

Addendum

The 4 cases reported in this series have been observed at monthly intervals. Since this paper was submitted for publication no evidence of recurrence of infection has been noted. The post-therapeutic observation periods are now seventeen, fourteen, thirteen and twelve months respectively.

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EXPERIENCE WITH PLASTIC TUBING IN PROLONGED INTRAVENOUS THERAPY*

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BOSTON

THIS paper summarizes our experience in using intravenous intubation in chronically ill patients for continuous or repetitive venoclyses. It is our impression that this method has a definite adjunctive value in hospital therapy and that it saves patients considerable hardship and renders less difficult the work of physicians and nurses in the management of the chronically ill.

This method is well illustrated in our treatment of a 35-year old woman with Marie–Strümpell arthritis. This patient had undergone 6 unsuccessful arthroplasties in the past and was bedridden. She entered the hospital with chronic pyelonephritis and renal calculi. She had intermittent episodes of renal infection resistant to therapy, continuous nausea, vomiting and intractable anorexia.

It was necessary to feed her parenterally; the poor condition of her veins made this task an ordeal for both patient and physician. Finally, a polyethylene tube was inserted in her right femoral vein and solutions of glucose, saline, amino acids, whole blood, blood plasma, serum albumin, alcohol, procaine and other medications were given by this means over a period of twenty-seven days. At the end of that time the tube was pulled out accidentally without hemorrhagic complications but was reinserted and remained in use for an additional 103 days, after which the patient died of an extrahepatic obstructive jaundice. Post-mortem examination revealed no clot formation in the vein around the tubing.

A number of references to the use of polyethylene tubing for intravenous therapy have been reviewed by Duffy, who reported the first extensive series of cases so treated.‡ His experience was gained in the treatment of 72 surgical patients; the longest period of intubation was thirty-nine days. There were 6 minor reactions in 43 patients in whom jugular or femoral veins were used, as opposed to 10 local reactions in 18 patients in whom arm veins were intubated.

Method

The equipment for intravenous intubation includes:

1 ft. of polyethylene tubing with an inner diameter of .034" and an outer diameter of .050"§; a size 14 needle; a size 19 needle; a 5-cc. syringe; a suture kit; and novocain.

The procedure, slightly modified from that described by Duffy, is carried out under aseptic conditions. The femoral artery is palpated and a suitable area adjacent to the inguinal ligament and overlying the femoral vessels is prepared with alcohol and aqueous Zephiran. A finger is held on the artery while a skin bleb is made with novocain through a hypodermic needle over the femoral vein. Then an intravenous needle is used so that the depth of the anesthetized area includes the perivenous tissue. A pointed scalpel blade is then used merely to perforate the skin and a 14-gauge needle mounted on a 5-cc. syringe is inserted into the vein. The correct placement of the needle in the lumen of the vein must be identified by blood's being drawn back freely into the syringe. The needle is further introduced into the lumen of the vein, so that the tubing will slip in with ease. With a gauze pad placed around the shank of the 14-gauge needle to receive the blood that will flow from it, the syringe is separated from the needle and the plastic tubing is inserted from 6 to 8 inches into the vein. The 14-gauge needle is withdrawn over the tubing, care being taken to keep the tubing from pulling out as well. A 19-gauge needle is inserted into the distal end of the tubing. At this point either heparin can be injected into the tube and a cap applied to the distal needle, leaving the tube ready for future use, or an intravenous infusion may be started. Lastly, the tubing is secured by a purse-string suture around the point of entrance into the skin and by a second suture securing a loop (Fig. 1).

The tube is then ready to function for an indefinite period of time. The only necessary precaution is that the tubing be kept filled with heparin when no infusion is being made. This is accomplished by injecting 0.5 ml. of heparin into the tube before placing the cap on the needle inserted into the external opening. Continuous therapy can be carried out or the tube may remain idle for any interval of time. We have reinfused with ease after an interval of two weeks, during which time the tube had remained filled with heparin.

Results

The femoral vein of 23 patients was intubated with polyethylene tubing. The left femoral vein was used in 5 cases and the right femoral in 18.

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‡Duffy, B. J., Jr. Clinical use of polyethylene tubing for intravenous therapy: report on 72 cases. *Ann. Surg.* 130:929-936, 1949.

§Tubing obtained from Clay–Adams Company, Incorporated, New York.

The diagnoses of the patients included plasma-cell myeloma, carcinoma of the cervix, neurogenic sarcoma of the kidney, malignant lymphoma, exfoliative dermatitis, generalized carcinomatosis, hypertensive arteriosclerotic heart disease, astrocytoma, giant-follicle lymphoma, carcinoma of the breast, chronic lymphatic leukemia, Marie-Strümpell arthritis, carcinoma of the ovary, malignant synovioma, cancer of the pancreas, Hodgkin's disease and essential hypertension.

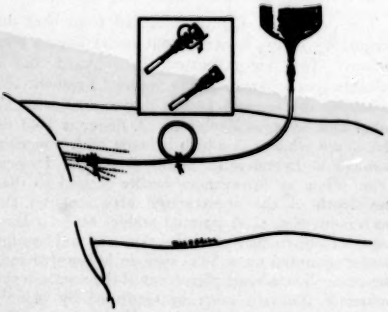

FIGURE 1. *Final Arrangement of Intravenous Infusion with Indwelling Polyethylene Tube and Capping when Tube is Out of Use.*

Catheter may be connected to tube of regular intravenous set.

The length of time of untubation varied from 1 day to 130 days. In 7 patients the intravenous tubing was left in place for more than 2 weeks. No more complications occurred in these long-term intubations than in the patients who were intubated for shorter periods of time. The only serious complication possibly referable to intravenous tubing was one thrombosis of distal leg veins occurring below the site of the tube on the eleventh day. Ten autopsies were performed on patients who had carried intravenous tubes for more than 1 week; clot formation around the tube was found in 2 cases. There had been no clinical manifestation of this, and no pulmonary emboli were found at autopsy. Approximately 850 liters of various fluids were given through indwelling intravenous tubes. We have estimated that about 450 venipunctures were avoided by the 23 intubations. In addition to this, the intrafemoral tube did not interfere with the patients' getting into and out of bed.

No difficulties were encountered in administering whole blood or plasma through indwelling tubing. Withdrawal of blood, however, was found to be impossible in most cases.

CONCLUSIONS

The use of polyethylene tubing for prolonged periods of intravenous therapy is a practical and reasonably safe procedure that saves the patient from considerable discomfort and facilitates the nursing problem. With proper technic, the time during which such indwelling tubes are well tolerated is considerable. Only one tube had to be removed because of a complication (possibly unrelated), and in one case intubation was maintained for 130 days.

ADDENDUM

Eighteen additional cases have been studied since this paper was written. Eight of these catheters were inserted into the left and 9 into the right femoral vein. The tubing was left in place for from two to eighty-eight days, 12 of them remaining in place for more than two weeks.

In the total group of 41 patients there were 3 cases of clinical thrombosis, 1 being septic and causing a septic pulmonary embolus, nonfatal, in a patient with a fecal fistula that contaminated the tubing. Eighteen autopsies were performed, revealing tenacious clot formation around the tubing in 5 cases, — but patent veins. Approximately 840 venipunctures were avoided, and 1229 liters of fluid were administered through the tubing.

REFORMATION OF AN OVARIAN DERMOID CYST*

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BOSTON

IN A previous paper entitled "Ovarian Conservation during Surgery"[1] particular attention was paid to bilateral ovarian dermoids and ovarian endometriosis. Two patients were reported therein who had bilateral ovarian dermoid cysts and in whom at operation a piece of normal-appearing ovary was preserved. In both cases this small piece of tissue, about half the size of a dime, was salvaged from the left ovarian cyst and was able to produce normal, regular periods. One of these 2 patients has not married. The other has married and has been delivered of 3 healthy, well-formed babies — on October 24, 1940, December 22, 1944, and October 13, 1946.

The first operation was performed on this patient on January 23, 1939, at the Mount Auburn Hospital. The pathological report read as follows:

> One specimen (right ovary) consisting of an encapsulated structure, roughly round, measuring 7 by 5.5 by 5.5 cm., is pale, yellowish pink. Along one side is a scarred projecting nodule, suggesting ovarian tissue. Section through this reveals a small follicular cyst (regressing corpus luteum). Section through the large mass shows a cavity filled with cornified epithelium. This can be peeled with some difficulty from the wall, leaving a smooth glistening surface. At one point there is a small bony, hard spicule. At another there is a small cyst filled with gelatinous mucus-like material. The gross diagnosis is epidermoid cyst of the ovary.
>
> The second specimen (left ovary) includes a similar cyst, which is roughly round, rather soft and buttery. There is one small, bare area. The wall measures 0.1 to 0.2 cm. in thickness. The cyst is filled with buttery white material that can be easily removed, leaving a clean surface with the exception of one point, where there is a projecting nodule from which a large tuft of black hair protrudes.
>
> The microscopical diagnosis of the first specimen (right ovary) is epidermoid cyst of the ovary, with a small follicular cyst, and that of the second (left ovary), dermoid cyst showing skin and skin appendages, cartilage, smooth muscle and abundance of myelinated and nonmyelinated nerve fibers; ganglion cells of the sympathetic system. There is no evidence of malignant change.

In order to emphasize its size, the description of the residual piece of ovarian tissue is repeated. It was less than half the size of a dime. This small portion of normal-appearing ovary was large enough to function in such a way that the patient had normal periods at regular intervals and three pregnancies after operation in 1939. The patient was 28 years old at the time of operation. The last child was delivered on October 13, 1946.

Frequent vaginal examinations were made after the last delivery. No abnormalities were found until March 2, 1948, about nine years after the operation. The uterus at this time was normal in size and position. A boggy mass about the size of a fist was present in the left vault. It was diagnosed as an ovarian cyst. Since the patient had had no symptoms referable to, or changes in, her menses, she was advised to return for another examination in a month. However, she did not return until August 17, 1950, at which time she was 40 years old. She stated that she was "troubled by a great deal of pressure inside the abdomen." The only alteration that she had experienced in her periods was a "heavy flow" two months previously. Her only other complaint was referable to occasional hot flashes.

On this date vaginal examination showed the uterus to be about normal size. The mass in the left vault felt tense rather than hard and seemed to be about the size of a grapefruit. She now agreed to have an operation performed; this was carried out on August 24, 1950, at the Booth Memorial Hospital. The left ovary was shown to be enlarged. It resembled a dermoid cyst. It was larger than a fist. The pedicle was fairly long and the ovary was twisted on it so that the cyst filled the posterior cul-de-sac. The veins in the left broad ligament were markedly enlarged, almost to the diameter of a fountain pen. Several small adhesions were present between the ovary and the sigmoid. The right tube and ovary were absent, having been removed in 1939. The operation consisted of a panhysterectomy and left salpingo-oophorectomy.

The pathological report read in part as follows:

> The left ovary is almost completely replaced by a cyst 8.0 by 5.0 by 3.5 cm. Section through the cyst presents a yellow, greasy material including numerous hairs and is lined by a smooth wall. The ovary is 2.0 by 1.5 by 1.0 cm. and is yellow and cerebrate. Section reveals smooth-walled cysts, some containing clear fluid and some containing clotted blood.
>
> Diagnosis: Ovary with dermoid and follicular cysts, corpus luteum.

After this operation the patient made an uneventful recovery and was re-examined on November 1, 1950, at which time she complained only of flashes, averaging one to two a day.

SUMMARY

This paper is presented to supplement previous studies in this series and to emphasize the fact that conservative ovarian surgery can be followed by excellent results, as in this instance, by salvaging a small piece of normal-appearing ovary. This patient subsequently married, had three normal children and was free of menopausal symptoms for nearly twelve years.

Also included is a report of the reformation of an ovarian dermoid cyst from a piece of ovarian

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tissue no larger than half the size of a dime that was "saved" during the process of removal of large bilateral ovarian dermoid cysts at a previous operation.

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MEDICAL PROGRESS

COARCTATION OF THE AORTA*

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COARCTATION of the aorta, although it has long been recognized, was regarded merely as a curious anomaly until 1944, when Crafoord performed the first operation for its relief. However, this successful operative treatment was the result of a number of years of investigation, during which the feasibility of such an operation had been demonstrated.

Blalock[1] had shown in 1932 that dogs will not survive an acute occlusion of the thoracic aorta and that the average duration of life after the occlusion is about three hours. However, in 1942, Owings[2] found that a multiple-stage progressive occlusion and eventual complete division of the thoracic aorta is tolerated fairly well by animals, who develop an extensive system of collateral arterial pathways similar to that seen in human cases of coarctation. Blalock and Park,[3] in 1944, performed a series of one-stage complete divisions of the aorta in dogs but in the same procedure severed the left subclavian artery several centimeters above its origin and used this vessel to bridge the gap between the proximal and distal segments of the aorta. Almost one fourth of their animals survived indefinitely after this procedure, but it was also found that extensive collateral pathways did not develop in these animals.

Simultaneously, the observations of Crafoord and Nylin[4] in Sweden had also indicated that a surgical attack on the problem of coarctation was feasible. In 1935 and 1936, Crafoord had discovered that the flow of blood to all the viscera could be completely interrupted for as long as twenty to twenty-five minutes with no subsequent signs of organic damage, provided that an adequate cerebral circulation was maintained. On the strength of this observation, he once completely occluded the aorta of a human patient for twenty-seven minutes during the performance of a difficult division and suture of a patent ductus arteriosus.

With this knowledge, and considering the fact that patients with coarctation have a well developed collateral system not possessed by normal persons, he thought that it might be possible to occlude the aorta for longer periods in order to satisfactorily repair a coarctation. Accordingly, he operated on a human patient on October 19, 1944 — the first such procedure ever attempted — and succeeded in removing the area of constriction and anastomosing the ends of the aorta. The patient survived the procedure well, subsequently being relieved of all his symptoms.

Gross and Hufnagel,[5] meanwhile, had been working on the same problem in this country, developing a technic for the operation very similar to that devised by Crafoord. Gross first successfully performed the operation on July 6, 1945. The good results obtained from surgical treatment in these and other patients have led to its universal acceptance.

The following is the case history of one such patient.

Case Report

W. S. (U. H. 299-786), a 12-year-old boy, was admitted to the University Hospitals of Cleveland on August 29, 1950, with a complaint of moderate dyspnea on exertion noted since an illness four years previously. At that time he had contracted a severe throat inflammation, which was seen by the family physician and called a "strep. throat." One week later he suddenly broke out with a fine red macular rash over the trunk and simultaneously developed a low but continuous fever. The day after the onset of the rash, a red, painful swelling appeared in both wrists, and soon afterward he began to feel pain in both ankles. No other joints were involved at any time. The fever that had begun simultaneously with the rash continued for about two weeks without much change; however, neither the patient nor his mother could recall either the peak or the average temperature during this period. Accompanying the fever was a rapid pulse of about 125 per minute, which, like the temperature, remained elevated for some time. The family doctor, on being called again, diagnosed the ailment as rheumatic fever and put the patient on strict bed rest, which was continued for nine or ten months. At no time during the onset or course of the illness did the patient experience any epistaxes, nausea or vomiting; he could not remember any shortness of breath or easy fatigability.

At the end of the period of enforced rest, the family physician informed the parents that the patient had a bad heart

*The Prize Essay for 1951.

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murmur, stating that it was due to residual rheumatic damage. Since the illness, however, the patient had been perfectly well except that he sometimes felt "all out of breath" after riding his bicycle up a hill or other moderate exertion; his mother stated that she had occasionally noted a slight cyanosis of his lips and buccal mucosae. There were no other symptoms. Shortly before his admission to the hospital the family physician had discovered a marked disparity between the blood-pressure readings obtained from both the patient's arms and, noting that the femoral and dorsalis-pedis pulses were very feeble, had suspected the presence of a congenital malformation.

Physical examination disclosed a well developed, moderately obese but rather pale boy who did not appear acutely ill. He measured 161 cm. in height and weighed 64 kg. The temperature was 36.6°C., the pulse 42 and the respirations 16. The blood-pressure reading obtained from his left arm was 140/94; that from his right arm, 82/70. Readings were difficult to obtain from his legs, but a systolic pressure of 90 mm. was recorded in both legs by some observers; the diastolic pressure could not be determined. The skin was warm and moist, — pale over the face and hands. There was no cyanosis of the nail beds or lips. The chest was symmetrical, the lungs were clear and intercostal pulsations were not detectable. The heart was distinctly enlarged, the apex lying in the area of the fifth intercostal space at the anterior axillary line, 12 cm. from the midsternal line, and showing a forceful apex beat. There was a normal sinus rhythm with a loud harsh midsystolic murmur, loudest over the second and third intercostal spaces at the left sternal margin, but also heard loudly over the apex and aortic area. The radial pulse was strong in the left arm but faint in the right arm; the dorsalis-pedis pulses were very faint bilaterally, and no posterior tibial pulses could be palpated. There was no clubbing of digits and no dependent edema.

Examination of the blood on admission showed a red-cell count of 5,470,000, a hemoglobin of 13.8 grams and a white-cell count of 5700. The Kline test was negative. The urine had a specific gravity of 1.012, a pH of 7.5, no protein or sugar and 0 to 1 white cells per high-power field. The electrocardiogram taken on admission showed an abnormally tall T wave in Lead 1, prolonged electrical systole (K = 0.47 sec.) and abnormal notching of the QRS complex in the limb leads. Simultaneous sound tracings showed a systolic murmur over the entire precordium. Oscillometric tests indicated that good pulsations were present in the left arm but very small pulsations were present in the right arm and both legs.

Because the physical findings strongly suggested the presence of a coarctation of the aorta, angiocardiography was undertaken in an attempt to visualize the deformity. The films demonstrated a normal flow of dye from the superior vena cava into the right side of the heart and thence through the pulmonary arteries. The aorta was found to opacify in the usual time, and the coarctation was grossly visible at the level of the fourth thoracic vertebra, taking the form of a deep notch in the posterior surface of the aorta. A definite post-stenotic dilatation of the aorta was visualized. Of interest in this case was the fact that the left subclavian artery was opacified one second before the right subclavian. The right carotid artery was normal in size and opacified simultaneously with the left carotid. The left ventricle, when opacified, appeared enlarged, and its wall was seen to be definitely thickened. No explanation could be given for the delayed circulation in the right subclavian artery.

An operation was performed on September 6, 1950. Under endotracheal ether-oxygen anesthesia the patient was placed on his right side with the left arm flexed and abducted over his head. An incision was made over the left fourth rib and the rib was resected for most of its length. The left lung was collapsed and retracted to expose the aorta: the pleura overlying the aorta was opened and the aorta dissected free.The coarcted segment was identified just below the origin of the left subclavian artery. The ductus was patent, measuring about 3 mm. in diameter, and entered the aorta about 1 or 2 mm. distal to the point of constriction. A large intercostal artery also joined the aorta at this point posteriorly; this artery and the ductus were ligated and divided. Several small bronchial arteries anteriorly were ligated and cut, but all other intercostal arteries were preserved. When the coarcted segment was completely freed, clamps were applied to the aorta and the segment was resected. End-to-end anastomosis of the segments of the aorta was carried out, using a continuous everting mattress suture, reinforced at several points by interrupted sutures. When the anastomosis was complete the clamps were slowly removed; during this process the cardiac rate and rhythm remained normal. There being no leakage from the suture line, the pleura was sutured over the aorta, the lung reinflated and the chest closed. The patient withstood the procedure well and was returned to the ward in good condition. Good dorsalis-pedis and posterior-tibial pulses were felt in both feet before he left the operating room.

The pathological report on the operative specimen was as follows:

> Received in formalin is a section of aorta measuring 1.2 cm. in outside diameter and 1 cm. in length. The wall is composed of homogeneous firm pale-gray tissue, 0.15 cm. in average thickness. The intima is smooth, glistening and pale gray in color. In the midportion of the specimen the lumen is abruptly reduced to a diameter of 0.3 cm. for a distance of approximately 0.2 cm. Three small branching blood vessels, the largest of which is 0.3 cm. in diameter, have been ligated with black silk.
>
> Diagnosis: Subintimal fibrosis of the aorta, clinically coarctation.

After the operation the patient was given 300,000 units of penicillin and 0.5 gm. of streptomycin twice daily for six days. His temperature rose to 38.5°C. on the afternoon of the operation and to 39° on the next day but then declined steadily, returning to normal on the fourth postoperative day. Urinary output remained good, a total of 1020 cc. being voided on the first postoperative day. An anteroposterior film of the chest made on the first postoperative day showed a pneumothorax on the left with about 60 per cent collapse of the left lung and some shift of the mediastinum toward the right. It was thought that there was fluid at the left base, this being verified on the same day by thoracentesis, which yielded 150 cc. of bloody fluid and about 300 cc. of air. Repeat films taken the next day showed clearing of the fluid shadows and almost complete disappearance of the pneumothorax, with the mediastinum in normal position. The sutures were removed on the fifth postoperative day and the patient was allowed to get out of bed on the eighth postoperative day.

A repeat examination of the blood on the fifth postoperative day showed a red-cell count of 4,800,000, a hemoglobin of 11.6 gm. and a white-cell count of 7200. Electrocardiograms taken on the seventh postoperative day indicated that the duration of the electrical systole had become normal (K = 0.37 sec.). Sound tracings recorded persistence of the systolic murmur over the entire precordium.

On the eighth postoperative day the blood pressure was: left arm, 120/98; right arm, 96 systolic by palpation; right leg, 126/98; left leg, 124/98. During the first three postoperative days the pressure in the right arm had been read at about 130/80 by several observers, but thereafter it declined and remained below 100 systolic.

When the time came for the patient to become ambulatory, he found some difficulty in walking and complained of a sensation of heaviness of his legs and feet. It was noted that he limped somewhat, swinging his right foot laterally when walking. However, his condition was otherwise very good, and he was discharged from the hospital on the tenth postoperative day, September 16, 1950.

At the time of his first visit to the Follow-Up Clinic, about one month postoperatively, he had no complaints. He had resumed normal activities, was eating well, and had no chest pain. The limp that had appeared after the operation had decreased considerably by this time. Blood pressures at this visit were recorded as: left arm, 130/88; right arm, 90 systolic by palpation; right leg and left leg, 130/100. At his next visit to the clinic, four months postoperatively, the pressures were: left arm, 135/95; right arm, 100/88; right and left legs, 130/90. The systolic murmur was still present and essentially unchanged.

The Pathologic Features of Coarctation

Bonnet,[8] in 1903, first classified coarctation in infantile and adult types, specifying that the infantile type is that in which the area of constriction

of the aorta is a rather extended one, lying between the origin of the left subclavian artery and the aortic insertion of the ductus arteriosus. The so-called adult type, on the other hand, is that type in which the constriction is sharply localized, either at the point of insertion of the ductus arteriosus or very close to it. The infantile type is rare, usually resulting in the death of the patient before the age of 2 years. The adult type, on the other hand, may be seen at any age, but since it is not incompatible with growth to maturity it is usually recognized in late childhood or early adult life.

In the adult type of coarctation, the annular constriction of the aorta is fairly typical, usually involving the superior, anterior and posterior aspects. The lower wall, at the insertion of the ligamentum arteriosum, may be regular or may be distorted convexly. The aorta is frequently dilated distal to the stricture, in many cases having a larger diameter in that region than it does proximal to the point of stricture.

When the aorta is opened, the coarctation is usually found to take the form of a diaphragm-like structure lying across the lumen, with a small aperture persisting in most cases. Edwards, Christensen, and others[7] describe a localized lesion that is frequently found in the wall of the aorta distal to the stricture, showing a corrugated patch elevated above the intimal surface, about 1 cm. in diameter. Microscopically, the lesion is seen to consist of localized fibrous thickening of the intima, below which the media shows atrophy and loss of elastic tissue. These workers believe that this area, which they name the "jet lesion," is the result of trauma produced by the jet of blood striking the aortic wall after passing through the constriction. It appears to be significant for two reasons. First, it may lie within that portion of the aorta that is anastomosed to the proximal segment during operation, in which case the atrophy and avascularity of the area may prevent adequate healing of the anastomosis. Secondly, the loss of medial elastic tissue in the area of the lesion may allow saccular aneurysms or, conceivably, dissecting aneurysms to originate at that point. These complications have occasionally been observed.

The so-called Skodaic hypothesis of the etiology of coarctation has been widely accepted in the past: namely, that the constriction results from an overgrowth into the aortic wall of the fibrous tissue that closes the ductus arteriosus. The popularity of this theory stems from the fact that the constricted segment of the aorta is most often located at the level of the ligamentum arteriosum, but it fails to explain those cases in which coarctation and patent ductus are present in the same patient or in which the constriction is located at some distance from the insertion of the ligamentum arteriosum. Actual evidence against the Skodaic hypothesis has been obtained by Edwards and Christensen through detailed study of microscopical sections. They found that the basis for the aortic narrowing is a peculiar deformity of the media, taking the form of a characteristic thickening located in the superior, anterior and posterior portions of the aortic wall, which projects into the lumen in the form of a curtain or diaphragm. This distinctive anomaly was found in all cases of coarctation at all ages, including infancy, and appears to be the fundamental defect. Evidence that this curtain is not related to the fibrotic process that closes the ductus was given by the findings in an infant who died at five months of age and was found at autopsy to have the adult type of coarctation. The medial curtain was present in this infant exactly as in older patients, but in this case the curtain was composed almost entirely of smooth muscle, with an almost complete absence of collagenous tissue.

In adolescent and adult patients an additional deformity is superimposed upon the medial anomaly mentioned above, which takes the form of a collagenous thickening and hypertrophy of the intima, especially prominent at the inner edge of the medial curtain. In longitudinal sections it has a triangular shape, the base resting on the margin of the medial curtain and the apex pointing toward the opposite wall of the vessel. It is avascular, being composed of collagen laid down in concentric layers. This intimal change, not seen in infants with coarctation, is interpreted as developing in response to the trauma produced by eddies of blood passing through the point of constriction. Thus, the authors believe that it can be said with assurance that the ligamentum arteriosum does not play any part in the etiology of coarctation, but the actual causes of the malformation are still unknown.

Bicuspid aortic valve is an anomaly that is frequently found in association with coarctation, but whether the bicuspid valve is congenital in origin or is acquired more frequently by such patients as a result of rheumatic inflammation is undecided. A division of bicuspid aortic valves into congenital and acquired groups purely on the basis of morphology is, of course, unreliable. Abbott,[8] in her study published in 1928, reviewing all the previously reported cases of coarctation, cited an incidence of 23.5 per cent among all patients with coarctation, but in subsequent studies the figure has gradually increased. Reifenstein, Levine and Gross,[9] in a study of 104 autopsied cases published in 1947, found that 42.7 per cent of these patients had had associated bicuspid aortic valves. They also found, however, that the incidence was 70 per cent in those patients who had both bacterial endocarditis and coarctation, indicating that the principal clinical importance of the bicuspid valves is that they are a more likely site than normal valves for the development of bacterial infection. They suggest that the majority of the bicuspid valves seen in association with coarctation may be acquired (rheumatic)

in origin and thus may be more vulnerable to infection.

Left-ventricular hypertrophy is found as the result of coarctation in almost every case, but the degree of hypertrophy does not appear to be related to the degree of aortic narrowing. However, definite relation[8] does seem to exist between the degree of constriction and the extent of the collateral circulation that is developed by the patient, as the collaterals are least evident when the constriction is moderate and are extensively developed if the stenosis is extreme or complete.

In those patients who do show an extensive development of collateral arterial channels, it is found that the subclavian arteries play the principal role in carrying blood from the aorta proximal to the constriction to the lower part of the body. The principal anastomotic channels through which this function is accomplished are:

The internal mammary-superior epigastric-inferior epigastric channel, through which arterial blood is carried directly from the subclavian arteries to the external iliacs. The importance of this channel is shown by two almost constant pathological findings in patients with coarctation: namely, that the internal mammary arteries are always dilated and tortuous and that the external iliac artery is generally larger in diameter distal to its junction with the inferior epigastric than proximal to it. This, of course, is precisely the reverse of the findings in a normal human body.

The connections between the internal mammary arteries and the descending aorta by way of the third through the twelfth intercostal arteries (the first two intercostals communicate between the internal mammary and the superior intercostal artery rather than with the aorta). This pathway is also of great importance, as the intercostals of adolescent and adult patients with coarctation are likewise constantly dilated and tortuous. It is this tortuosity that causes pressure atrophy of the adjacent ribs at the points where the loops of artery are in contact with the rib, thus producing the well-known roentgenologic sign of notching of the costal grooves.

The arterial networks around the scapulas, made up of the transverse cervical, transverse scapular and subscapular arteries and their branches. This network as a whole arises from the subclavian arteries and communicates by means of the intercostals with the descending aorta.

The vertebral arteries, arising directly from the subclavians, which communicate through numerous branches with the anterior spinal artery. This provides the principal blood supply for the spinal cord; but it also communicates via the intercostal arteries with the descending aorta. A relatively little known fact is that the anterior spinal artery is also frequently dilated and tortuous, particularly in the cervical and thoracic regions.

Other very minor collateral channels, such as the superior intercostal artery (a branch of the costocervical trunk), the lateral thoracic artery (branch of the axillary) and the lumbar arteries, which are analogous to the intercostals.

However, depending on the type of coarctation present, the collaterals may vary from side to side, and this difference may in some cases be very striking. For example, if the site of the coarctation lies between the left common carotid and the left subclavian, the chief load of collateral function falls on the right subclavian and its branches.[7] Conversely, in those cases (such as the case cited above) in which the constriction at the ligamentum arteriosum is associated with stenosis of the right subclavian artery at its origin the major collateral function is borne by the left subclavian and its branches.

The Causes of Death in Coarctation

The reviews, previously mentioned, by Abbott[8] and by Reifenstein, Levine, and Gross,[9] showed a similar distribution of the causes of death in patients with coarctation. In the more recent of these two series,[9] it was found that 61 per cent of the patients had died before or during the fortieth year of life. Seventy-four per cent of the patients had died of causes associated directly with the condition, whereas 26 per cent had died of "incidental" causes such as pneumonia, uremia, malignant diseases, trauma or coronary-artery disease. Rupture of the aorta was found to be the most frequent, causing death in 23 per cent of the patients. Of the 104 patients in the series, 19 showed rupture of the ascending aorta, with an average age at death of 30 years. In 5 cases the rupture was distal to the constriction; in these the average age was 19 years. Those patients with rupture of the ascending aorta had shown the usual symptoms of dissecting aneurysm, and death was rapid in every case.

Bacterial endocarditis and aortitis, together causing 22 per cent of the deaths, commonly affected the aortic cusps, but in some cases only the root of the aorta was affected. Alpha-hemolytic streptococci were the commonest infecting organisms. The valve lesions resulted in marked aortic insufficiency, with high pulse pressures, typical murmurs, cardiac hypertrophy and associated vascular phenomena, whereas the symptoms of isolated aortitis resembled those of endocarditis but did not include the signs of aortic insufficiency.

Eighteen per cent of the patients in the series died in congestive failure, at an average age of 39 years. The remarkable feature common to these cases was the fact that almost all showed some associated abnormality that would also tend to

produce congestive failure, such as renal disease, chronic valvular disease or coronary disease. Thus it appears that patients with coarctation almost never develop congestive failure unless some additional strain is placed on cardiac function.

Intracranial vascular lesions caused 11 per cent of the deaths, the average age at death being 28 years. The most common of these lesions was ruptured aneurysm of the cerebral vessels, but several cases of subarachnoid hemorrhage occurred in which no aneurysm could be found. The aneurysms most commonly involve, or are situated near, the circle of Willis and on microscopical examination show a deficiency of medial tissue, — a finding consistent with the concept of their congenital origin. An interesting finding was the fact that systolic, diastolic and pulse pressures tended to be highest in those patients who died of intracranial lesions.

Clinical Features of Coarctation

The most obvious clinical signs in patients with coarctation of the aorta are those that result from the hypertension in the upper part of the body and from the difference in arterial pressures between the upper and lower parts of the body. Children and adolescents may have no symptoms at all if the degree of aortic constriction is not extreme, but later many of the usual symptoms of hypertension develop. These may include flushing, headaches, epistaxes and sensations of pounding in the head, which may be accentuated by stooping or bending over. The retinal arteries are commonly full and tortuous and may show nicking of vessels, retinal hemorrhages and so forth. Differences in blood flow between the upper and lower extremities are frequently the first clue to the presence of coarctation, since palpation of the femoral or dorsalis-pedis pulses in a young person with hypertension may frequently give the diagnosis. Blood-pressure readings may be unobtainable from the legs or in less severe cases may merely be lower than those from the arms. Frequently the patients notice coldness, pallor and numbness of the legs and feet; occasionally there may be pain, intermittent claudication and marked weakness. Gross[10] believes that the exercise-tolerance test is valuable in the diagnosis, for although a normal person will respond to moderate activity by an elevation of the systolic pressure of from 20 to 40 mm. a patient with coarctation will respond with extraordinary rises in the arm pressures — frequently as much as 100 to 150 mm. above the resting level.

Signs of the increased collateral circulation to the lower part of the body may occasionally be evident: for example, visible pulsations may be present along the collateral pathways, such as in the intercostal, suprascapular or superficial epigastric regions. In some patients there may be signs of differences in circulation to the arms, such as coolness or pallor of the arm receiving the lesser amount of blood, smaller pulses, lower blood pressures and, occasionally, numbness or tingling. These signs appear more commonly in the left arm, because of the fact that the constriction is not infrequently located proximal to the origin of the left subclavian, but may appear in the right arm if there is stenosis of the origin of the right subclavian artery.

A systolic murmur is almost invariably present and is generally heard all over the precordium but is loudest over the base. In many cases the murmur radiates to the back and may be heard just to the left of the thoracic spine. It is generally thought to be produced simply by the constriction; however, this is still undecided, as many cases with complete atresia of the aorta also have a systolic murmur. In such cases the murmur may be the result of associated valvular lesions, or of the deformity of the arterial tree produced by extensive collateral development. The murmurs having such a peripheral component are generally continuous in character, being accentuated during systole and dying off during diastole. A case of interest[9] is that of a 50-year-old man with complete aortic atresia who died of bacterial endocarditis of the aortic valve. He was reported to have had only a diastolic murmur. However, a diastolic murmur does not occur in uncomplicated coarctation; when present it is an indication of aortic valvular disease, — especially bacterial endocarditis, — or of a patent ductus arteriosus.

The principal roentgenologic sign of coarctation is the so-called "notching of the ribs" sign, which when seen is almost always pathognomonic. Actually, the erosion does not occur along the inferior aspect of the rib but along the lower margin of the body of the rib, where the body of the rib meets the narrow bony ridge that forms the posterior wall of the costal groove. "Notching of the costal grooves" would thus be a more correct term. This sign may also occur in neurofibromatosis when the intercostal nerves are involved or may be produced by vascular lesions of the thoracic wall, such as congenital arteriovenous fistulas. In patients with coarctation it may be overlooked, or it may not be evident in young patients in whom the extreme degree of tortuosity of the intercostal arteries has not yet developed. Similarly, it may not be obvious in adult patients in whom the coarctation is not sufficiently severe to require the development of greatly dilated intercostals. In a series of 90 patients reported by Pugh,[11] the youngest showing the notching sign was 8 years old.

Other confirmatory signs that may appear in x-ray films of the chest are a lack of prominence of the aortic knob, left-ventricular hypertrophy, an occasional visible notch in the aorta and unusual clearness of the aortic window in the left anterior oblique view.[12] However, the most valuable method for accurately outlining the point of aortic con-

striction is the technic of angiocardiography developed by Robb and Steinberg,[13] by which the chambers of the heart and the great vessels may be visualized radiographically a few seconds after the intravenous injection of 30 to 45 cc. of a 70 per cent solution of iodopyracet ("diodrast"). Gross[10] has found this method rather disappointing, however, since the dye is frequently too diluted by the time it reaches the aortic arch to outline the aorta satisfactorily. He prefers direct injection of diodrast into the arterial side of the circulation, through a fine catheter which is threaded into the left axillary artery and backwards into the root of the aorta. The dye thus reaches the aorta in high concentration and affords excellent visualization.

Hypertension Accompanying Coarctation

There has been much debate in the past about the mechanism by which hypertension is produced in patients with coarctation, for ever since the experimental reproduction of essential hypertension by Goldblatt it has been suggested that the constriction in the aorta may act as a Goldblatt clamp, producing renal ischemia and the accompanying hypertension. However, in most patients who have coarctation the systolic arterial pressure in the arms is about 160 to 180 mm. of mercury, whereas the diastolic is seldom higher than 90 mm. This range is of the type considered indicative of resistance in the larger arteries, rather than of the type characterized by higher diastolic pressures and lower pulse pressures, which are thought to indicate arteriolar resistance. The "essential" hypertension produced by renal ischemia is, of course, of the latter type; if the fundamental cause were the same in both the hypertension should be present throughout the body rather than only in the arms. Furthermore, if a uniform arteriolar constriction existed throughout the body the flow of blood through the upper extremities should be greater than normal and that through the lower extremities should be less than normal, exactly as if arteriolar tone throughout the body were normal. It was found by Wakim[14] that the differences in resting blood flow through the upper and lower limbs of normal persons and of patients with coarctation were insignificant and by Bing and others[15] that the cardiac output in such patients showed no significant differences from that in normal persons. In addition, Blumgart, Lawrence and Ernstene[16] found the arteriolar pressure, as measured by the histamine-flare method, to be approximately normal in their two patients with coarctation. All these facts are consistent with the hypothesis that the hypertension is more directly related to the resistance offered by the stenosis than to renal mechanisms. Further proof has been furnished by the observation that arterial pressures in the arms and legs tend to equalize after surgical correction of the stenosis.

Considerations in Surgical Treatment

The technic of the operation for this condition has been discussed in detail by Crafoord and Nylin,[4] Gross,[10, 17, 18] and others[19] and need not be described here. However, Gross emphasizes a few general principles that are of importance in the surgical treatment.

Intratracheal anesthesia is essential in this operation because of the open chest wall. Cyclopropane may be rather dangerous if used for the entire operation; ether in a closed system appears to be the most satisfactory.

Careful attention must be paid to the replacement of the blood lost during the operation. The loss may be pronounced during the opening of the chest because of the greatly increased vascularity of the chest wall, and injury to any of the large dilated collateral vessels around the aorta may result in a serious hemorrhage. Gross recommends that dry sponges and packs be used and weighed after use in order to determine the amount of blood contained in them. This amount, together with that in the suction-apparatus bottle, will give a rough estimate of the blood loss and enable the surgeon to carry out a more effective replacement therapy. The intravenous administration of glucose during the long operation will also help to maintain the patient in a stable condition.

It is commonly believed that it is wise to make an effort to preserve as many of the collateral vessels around the site of constriction as possible. However, the collaterals should always be sacrificed if it appears necessary to do so in order to obtain the best possible anastomosis of the ends of the aorta.

Crafoord, in his pioneer work, used Carrel's method of arterial suture,[20-22] which approximates all layers of the aortic wall to each other by means of a continuous over-and-over suture penetrating the adventitia and media but not the intima. Gross, however, thinks that this method is unsatisfactory in that leakage from the suture line frequently occurs and that occasionally there may be complete disruption or the formation of dissecting aneurysms at the suture line. He prefers a continuous mattress suture that penetrates all three layers and everts the cut edge of the aortic wall, approximating intima to intima, and states that he has found this type of suture completely satisfactory.

Older patients are generally unsatisfactory subjects for surgical treatment, because of the greater frequency of sclerotic changes in their vessel walls. Furthermore, other complications such as advanced cardiac enlargement, myocardial damage and decreased cardiac reserve are more likely to be present in such patients. Some excellent results have been obtained from surgery in patients in their late twenties or even older, but the most desirable age for operation appears to be in the second decade. Very young children are also poor subjects, as

their aortas are not large enough to be worked on with facility, making the operation technically more difficult, and the risk is probably higher because the collaterals are not well developed. In addition, the possibility exists that the aortic lumen established at the site of anastomosis may not keep pace in growth with the rest of the aorta and the constriction thus may again develop as the child grows older. Brooks,[23] however, found that if resection of a segment of aorta followed by anastomosis is performed in young puppies, the diameter of the lumen at the point of anastomosis does grow in size but not so much as the remainder of the aorta. He found that the degree of constriction at the anastomotic site was about 20 per cent of the expected diameter after the puppies reached maturity.

In general, a high degree of hypertension does not disqualify a patient for operation, nor does it indicate that there will be an unsatisfactory result. However, a long-standing severe hypertension, especially beyond the second decade of life, will almost certainly increase the operative difficulties. The hypertension eventually leads to a loss of elastic tissue and fibrosis of the aortic wall; hence, after resection of the coarctation it may be difficult to approximate the ends of the aorta to obtain a satisfactory anastomosis.

There have been reports of successful surgical treatment of the infantile type of coarctation as well as of the adult type. Johnson and Kirby,[24] Clagett[25] and others have divided the dilated left subclavian artery several centimeters distal to its origin, turned it down and anastomosed it to the distal segment of aorta. In many of the cases the subclavian is so enlarged that its diameter closely approximates that of the aorta and end-to-end anastomosis is thus feasible. Gross has treated such patients by using a preserved segment of aorta as a graft to bridge the long defect in the patient's aorta; the results of this procedure have appeared to be very good. Thus it appears that if early diagnosis is made almost all patients with coarctation will in the future be able to receive the benefits of surgical treatment.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 37291

PRESENTATION OF CASE

A twenty-one-year-old man was brought to the hospital in an ambulance.

On the day of entry, the patient fainted at work but revived spontaneously and went to the nurse's office, where he again collapsed. Investigation was begun because a ventricular tachycardia of 300 was noted, with a blood pressure of 70 systolic, 50 diastolic.

The patient's past history revealed no evidence of polyarthritis, chorea or acute infections. He took no medication other than an occasional aspirin. The patient frequently drank 10 to 15 beers. Three months previously he passed a naval physical examination. Three weeks prior to admission, pain and swelling in the right elbow was treated by his physician with hot packs. On the evening before entry he had consumed about 15 beers, and therefore paid little attention to a dull pain just to the left of the xiphoid on the morning prior to the first fainting attack.

Physical examination showed a pale, well developed young man with clammy extremities. The right ear was lacerated. A persistent cough productive of pink, frothy, watery fluid was noted during examination. The neck veins were not distended. Numerous moist rales were heard throughout both lung fields. The cardiac apex was percussed 7.5 cm. from the midsternal line; the rapid heart sounds were obscured by noisy respirations. No murmurs were audible. Slight epigastric tenderness was noted on abdominal palpation, although there was no splinting or rebound tenderness. The liver edge was not felt.

The temperature was 99°F., the pulse 120 and the respirations 28. The blood pressure was 100 systolic, 70 diastolic.

The urine sediment contained many white cells and numerous clumps suggestive of bacteria, although culture was negative. Examination of the blood revealed a hemoglobin of 16 gm. and a white-cell count of 19,800, with a normal differential. Blood-serum studies showed a sodium of 122.6 milliequiv., a chloride of 87 milliequiv., a potassium of 4.6 milliequiv. and a carbon dioxide of 27 milliequiv. per liter. The nonprotein nitrogen was 40 mg., the fasting blood sugar 113 mg. and the cholesterol 155 mg. per 100 cc. The antistreptolysin titer of 100 to 250 was within normal range. The stool was guaiac negative. The electrocardiogram showed a ventricular tachycardia of 230, which slowed to 120 per minute after the administration of 10 cc. of Pronestyl, but showed a pattern of right-bundle-branch block.

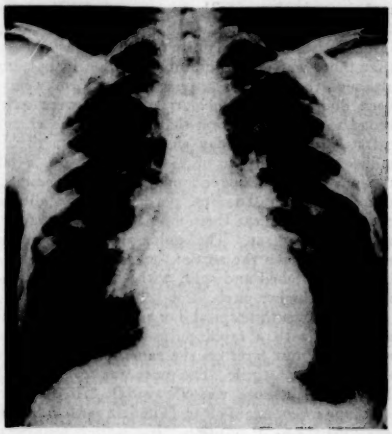

FIGURE 1.

The patient received 200 cc. of blood on entry to the Emergency Ward, and the lacerated ear was sutured under local anesthesia. Pronestyl and digitalis with oxygen and morphine as adjuncts gave general circulatory improvement with rapid clearing of pulmonary edema. On the next evening pulmonary edema recurred, although the heart rate remained at 120 per minute, with a gallop rhythm. The neck veins collapsed when the head was raised more than 45°. The left cardiac border was now percussed 11 cm. from the midsternal line. Repeated electrocardiograms showed essentially no change. On the second hospital day coarse rhonchi were heard throughout the chest, most clearly at the right base. The left upper lobe seemed somewhat

less aerated than the rest of the lung. Toward evening of the same day grossly bloody sputum was expectorated. Examination of the legs was unremarkable. An x-ray film of the chest showed increase in hilar markings but no definite areas of consolidation (Fig. 1). Intramuscular administration of cortisone was begun, with an initial dose of 300 mg. Thirty hours later the patient appeared comfortable and felt quite well. The temperature was normal and the blood pressure was 110 systolic, 70 diastolic. The heart was still enlarged to 10 cm. to the left of the midsternal line, and the heart sounds were now of good quality. The lungs showed only a few rhonchi at the right base, which cleared on coughing. Blood chemical levels remained essentially unchanged during administration of the drug. An electrocardiogram again showed a normal sinus rhythm of 85, a PR interval of 0.21 second and a QRS interval of 0.16 second; the Q waves in Leads 1 and V_6 were quite broad. It was thought that there was no significant alteration in pattern, although the Q waves in Leads 1 and V_6 may have been due to septal depolarization but were quite broad to be explained on that basis. Blood chemical studies the next day showed a sodium of 136 milliequiv., a chloride of 95 milliequiv. and a potassium of 4.2 milliequiv. per liter. The sedimentation rate was 0.6 mm. per hour. The clinical course over the next three days was one of remarkable improvement. The pulmonic second sound was greater than the aortic; the mitral sounds were loud, low-pitched and split, with the second mitral sound of a higher pitch.

On the seventh hospital day a rise in temperature associated with a rapid pulse and eosinophil rise was noted, but later on the same day the patient again became afebrile. The pulse was regular at 72. The blood pressure was 95 systolic, 70 diastolic. The lungs were again clear. The left cardiac border was unchanged in position. The second sounds at the base were split, with slight accentuation of the pulmonic. A prominent protodiastolic gallop was present; it was followed by a Grade I rumble with slight presystolic crescendo, audible over the left precordium. On the following day the liver edge was believed to be 2 fingerbreadths below the costal edge. The patient complained of steady sharp nonradiating midepigastric pain without localizing abdominal signs. A gastrointestinal series demonstrated prominent folds suggestive of gastritis, although no ulceration was demonstrated. The pain continued throughout the remainder of the hospital course. Cortisone dosage was increased to 300 mg. and then maintained at an average of 150 to 225 mg. daily. He showed some signs of improvement, but within three to four days his general condition appeared to be deteriorating. The protodiastolic gallop became increasingly prominent and the heart remained enlarged.

On the twenty-fourth hospital day a midsternal ache was noted and gross blood was expectorated. Leg examination was negative, and the chest was clear except for a few moist basal rales. During the day the temperature rose to 104.6°F., accompanied by many moist loud inspiratory and expiratory rales heard over the right anterior chest up to the fourth rib; an area of dullness was present over the right upper lobe anteriorly. Tachycardia began with the febrile state at a rate of 132 per minute. A white-cell count was 13,000, rising to 22,000 in twelve hours. Bilateral common-femoral-vein ligation and interruption was done under local anesthesia, although no clots were found in the veins. On the morning following this procedure the patient complained of severe chest pain anteriorly and felt nauseated. The nurse found no pulse or discernible blood pressure. The heart was beating irregularly at 25 to 28 per minute and the extremities were cyanotic. Epinephrine, given intravenously, increased the heart rate to 48 per minute. An electrocardiogram was then taken; it showed paroxysmal auricular tachycardia and auriculoventricular dissociation, with changing ventricular rate.

A few hours later the patient complained of severe precordial pain. The heart sounds were inaudible. Intracardiac adrenalin injections were of no avail, and he died.

Differential Diagnosis

Dr. Lewis Dexter*: Thank you for the privilege of allowing me to discuss this case at a Massachusetts General Hospital Clinicopathological Conference.

May I see the x-ray films?

Dr. Stanley M. Wyman: The series of film shows a changing picture. Initially the heart is quite large and perhaps appears smaller in subsequent examinations. There is rather pronounced hilar vascular engorgement, with pulmonary edema in the left lung centrally and to a lesser degree in the right. This cleared, but there was still some pulmonary congestion. The third examination (Fig. 1) shows the lung fields as still somewhat congested at the lung roots, but the peripheral lung fields look clear. On this examination the cardiac enlargement appears to be quite general, involving all chambers, but I would say particularly the ventricles. The right ventricle is definitely large, and the left is possibly also moderately enlarged. Then the heart started to get larger again at each examination and continued until on the last examination it is about as large as it was initially. On the last film there seems to be an additional rather homogeneous density in the right lower lobe, with its level adjacent to the major fissure. This is more than the general increase in pulmonary congestion that has occurred (Fig. 2).

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DR. DEXTER: That is this area here! I was hoping something like that would show up.

DR. WYMAN: A single film from the gastrointestinal examination shows no definite localized disease.

DR. DEXTER: Let me summarize very briefly. Here is a young man, twenty-one years old, who was previously well enough to pass a naval physical examination — and I need not remind you that that is quite a thorough examination. Without much warning and without any history of previous illness, he developed paroxysmal ventricular tachycardia and went into pulmonary edema and shock.

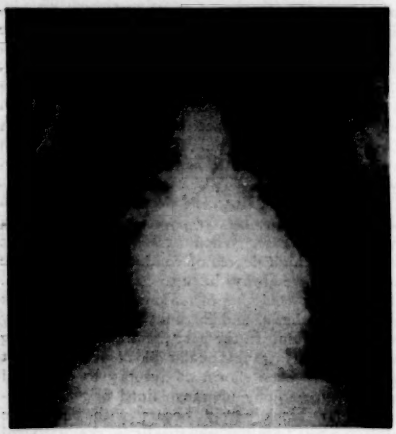

FIGURE 2.

The next day he had another episode of pulmonary edema, without paroxysmal tachycardia on this occasion. The electrocardiograms showed right-bundle-branch block. He had an episode of raising bloody sputum, and later in the course of the disease raised grossly bloody sputum. There were various changes in the lungs at physical examination, and then he had this vascular embarrassment at various times, which I assumed was due to pulmonary edema — and I assume that this area in the x-ray film is perfectly consistent with a pulmonary infarction. He responded very well to the administration of cortisone but then seemed to break through that therapy. Finally he had a terminal episode.

First of all I should like to discuss the episode of pain and swelling in the right elbow. Whether that followed the "ten or fifteen beers" and was traumatic, or whether it was possibly inflammatory, I cannot determine. I doubt that the physician would have put hot packs on the elbow if it were hot; therefore, I am inclined to believe that the pain and swelling were due to trauma. At any rate, I shall not consider that further in my discussion.

The patient was brought into the hospital because he had fainted twice at work. Wolff[1] pointed out a few years ago that as soon as a patient's heart rate goes over 180 to 200 he is prone to faint. I am not surprised that this patient, who had a rate of 300, had syncope.

Ventricular tachycardia in patients is usually associated with some sort of underlying heart disease, in contrast to auricular tachycardia, with which patients usually have otherwise normal hearts. In addition, he had numerous moist rales in both lungs — in other words, he had pulmonary edema. The pulmonary edema means to me that he did have some underlying disease on the left side of the heart. With ventricular or auricular tachycardia one should not go into congestive failure as rapidly as this patient did. The underlying heart disease may have been of the left ventricle; that is, of the heart muscle itself, of the aortic valve or of the mitral valve. I am puzzled by the right-bundle-branch block noted in the electrocardiogram. If that is a manifestation of something wrong with the right ventricle, which I think is a justifiable assumption, then it indicates that this patient possibly had right-ventricular hypertrophy. Moreover, when a patient has had a normal-sized liver that becomes enlarged, I think I must assume that the right ventricle has failed. But I also have to think in terms of something wrong with the left side of the heart. The most likely lesion that can produce this combination of findings is mitral stenosis, but mitral stenosis could not be severe in a man who survived at a pulse rate of 300; yet he had all the physical signs of mitral stenosis. I do not understand that very well. The grossly bloody sputum may have occurred as the result of mitral stenosis. In these patients it is often caused by pulmonary infarction, although occasionally it is caused merely by congestive failure.

I shall discuss the various possibilities that have occurred to me. What about the possibility of subacute bacterial endocarditis of an unusual sort? The only murmur heard was a Grade I, left-precordial diastolic rumble, with presystolic accentuation heard apparently on only one occasion. From the description, this is not diagnostic of any specific lesion. Bacterial endocarditis in the presence of a nonspecific type of murmur might be found in association with atrial septal defect, with which it is a very rare complication; a bicuspid pulmonic valve, which should not produce right-bundle-branch block; pulmonic stenosis, which I have never seen without a telltale murmur; and aortic stenosis. In the latter instance a murmur, initially absent, rapidly appears. A right-sided bac-

terial endocarditis might produce pulmonary infarction, as in this case, and the electrolyte disturbance in this patient may have been reflecting a renal embolic reaction. This reasoning is farfetched, however, and the absence of spiking fever, changing murmurs, anemia and splenomegaly and the whole clinical course, which is one of diffuse myocardial failure, do not suggest bacterial endocarditis in any way.

This man had a dull epigastric pain throughout the whole hospital course. I suspect that he may have had a pericarditis of considerable extent. However, for pain to be present for so long a time without going up into the shoulder or across the chest is unlikely — yet the epigastric pain was of sufficient importance that the physicians believed the patient ought to have a gastrointestinal series.

It seems to me that I must assume that he had a diffuse myocarditis of some sort. Fiedler's myocarditis, which is quite a rare disorder, is one possibility. Finland[2] was able to demonstrate the influenza virus in two cases. Although I have not heard of any case of Fiedler's myocarditis that had been treated with cortisone, I should suspect that it would not respond to cortisone. If you can judge by analogy with other virus diseases, when the virus is intracellular cortisone does not have any effect. This patient did respond to cortisone; at any rate, he was comfortable thirty hours after cortisone was administered.

He may have had one of the diffuse so-called collagen diseases, such as polyarteritis, which may have an extremely unusual group of manifestations. The manifestations of polyarteritis may merely be limited to the heart, without evidence of involvement of the lung, kidney and so on. In this patient there were no other manifestations of polyarteritis, such as joint symptoms and the whole list of other stigmata that one expects to find sooner or later. The patient did have low sodium and low chloride, which puzzles me very much and makes me suspect that there was something going on in the kidneys.

I think, statistically, that the most likely possibility is diffuse rheumatic carditis. This is the common myocarditis in this age group, and it may have a very masked form. The course that this patient ran, although not characteristic, was compatible in all ways with a diffuse rheumatic myocarditis. The points against it were the absence of joint symptoms and fever, the normal sedimentation rate and the lack of antistreptolysin elevation. One does not have to have any of these findings. The response to cortisone was typical. As you will recall, within thirty hours the patient looked well and his heart sounded normal. He still had a slight residual change in the heart. Rheumatic myocarditis alone will not explain this patient's death. I do not think it will explain the hemoptysis too well. It is perfectly possible for a patient with rheumatic carditis under control with a given regimen of cortisone to escape from the therapy even though the dosage is fairly high.

The episode causing his death and various episodes scattered through the course are not, in my estimation, compatible with simple uncomplicated rheumatic carditis. I am referring to the hemoptyses and the terminal episode. I must agree with what I think was going on in the minds of those who were taking care of him: that is, recurrent pulmonary embolisms. Whether it was an embolism that precipitated the original ventricular tachycardia I do not know. As a matter of fact I have never heard of ventricular tachycardia's being precipitated by a pulmonary embolus in man. I have produced it in dogs experimentally, however. The rest of the course — the hemoptysis, the congestion and so forth — are perfectly classical indications of pulmonary embolism. Then there was the wedge that was present in the x-ray films. I conclude that he had an active rheumatic fever with carditis, and recurrent pulmonary embolisms, which were the cause of death, aggravated by the underlying cardiac lesion.

Dr. Edward F. Bland: I do not know the diagnosis yet. As Dr. Dexter pointed out, this was a very puzzling case. When we see a young patient with such a high degree of conduction disturbance in the heart we always have to consider diphtheria. However, for a number of reasons we did not think he had diphtheria, and fortunately we do not now see it very often. In the past the majority of young patients with intraventricular block of this extent have usually been shown at autopsy to have had cardiac hypertrophy of unexplained origin. Intraventricular block rarely occurs with rheumatic fever — why, I do not know; but in the 300 fatal cases studied here and at the House of the Good Samaritan by Duckett Jones and me a few years ago, high-grade intraventricular block was not encountered in a single case.[3] This and the absence of significant murmurs led us to believe that the patient did not have rheumatic myocarditis. It was our final impression that he had long-standing unsuspected heart disease of undetermined nature and that the terminal illness must have been an acute inflammatory reaction in the myocardium, — maybe a recrudescence of obscure myocarditis that had smoldered in the past.

Dr. Marian W. Ropes: Our original belief was that this man's lesion was either rheumatic myocarditis or Fiedler's myocarditis. At first I favored rheumatic myocarditis on the basis of the joint involvement that had developed without trauma. However, when no murmurs developed and when I learned that ventricular tachycardia was uncommon in acute rheumatic myocarditis and much more likely in Fiedler's myocarditis, I began to turn

toward the possibility that this was idiopathic myocarditis of the so-called Fiedler type. The use of cortisone was based on the assumption that the idiopathic type of myocarditis might respond like rheumatic myocarditis. I think there was no question that it did respond. As Dr. Dexter said, when the terminal episode began he had shown evidence of escaping from the effect of cortisone. The nature of the pulmonary complication was not clear. At one time I considered the possibility of an inflammatory lesion in the lung similar to that seen in rheumatic infection. However, when the x-ray findings gave further evidence of pulmonary infarction, ligation of the femoral vessels was performed. The bundle-branch block occurred after Pronestyl had been given, and I wondered whether it could have been related to this drug. It is of interest that the right-bundle-branch block disappeared and left-bundle-branch block appeared in the terminal episode. In regard to the low sodium and chloride, we have no explanation for them. They came up rapidly to normal levels. I assumed that the abnormal values must have been related to the disturbance caused by the acute attack. I have no idea what that meant.

Dr. Daniel S. Ellis: Are there any suggestions about the acute upper-abdominal pain?

Dr. Ropes: There was some discussion about whether it could have been explained by congestion of the liver. We were never able to determine the cause of the epigastric disease. It was present throughout the course of the disease. At one time it extended up under the sternum and was increased with swallowing, so we thought it might be a manifestation of a mediastinitis.

Dr. Jacob Lerman: I think that in some cases of polyarteritis extensive involvement of vessels in the adrenals will occasionally be found and that there is a low sodium and chloride, based on adrenal insufficiency.

Clinical Diagnoses

Idiopathic myocarditis, severe, with cardiomegaly.
Pulmonary infarcts.

Dr. Dexter's Diagnoses

Active rheumatic fever with carditis.
Recurrent pulmonary embolism.

Anatomical Diagnoses

?Isolated myocarditis, ?idiopathic cardiac hypertrophy; with mural thrombus of left ventricle.
Hemorrhagic pulmonary edema, severe.
Chronic passive congestion of lung and liver, severe.
Infarction of left kidney and lung.

Pathological Discussion

Dr. Tracy B. Mallory: I am quite unable to make a diagnosis on this patient beyond the obvious fact that he had severe heart disease, but what the type of heart disease was I do not know. The heart was greatly enlarged, weighing 750 gm., a really large heart for a young man of twenty-one years. There was no pericarditis and no evidence of endocarditis. But there was a thrombus in the apex of the left ventricle such as often overlies a focus of infarction. However, no infarction could be discovered, and the coronary arteries were quite normal. A portion of this thrombus had eventually broken loose and served as an embolus, finally ending up in the left kidney, where an infarct was produced in the upper pole. Infarcts of the kidneys can occasionally be very painful, but one would not expect the pain to be epigastric. At the end of the gross portion of the autopsy the impression was that he had congenital idiopathic cardiac hypertrophy or perhaps some form of myocarditis.

Figure 3.

Section from the myocardium showed no evidence of acute inflammatory reaction; that is, there was no infiltration of polymorphonuclear leukocytes. There were, however, many foci from microscopic size up to 3 mm. where the muscle cells had disappeared and were replaced by loose connective tissue in which there were scattered lymphocytes and monocytes, some of which contained hemosiderin (Fig. 3 and 4). These areas were ill defined and merged with necrotic muscle fibers. Around these the muscle cells appeared large and swollen, with separation of the myofibrils and cross-striations more widely separated than usual, — the sort of appearance that one could expect with a severe intracellular edema, except that there was no vacuolization. Most of the nuclei showed degenerative changes such as pyknosis and swollen, distorted shapes. There was also a definite increase in interstitial fibrous tissue. No Aschoff bodies or anything simulating a rheumatic myocarditis was seen.

It forces us to consider the very interesting possibility that cortisone may on occasion completely abolish the histologic evidence of an inflammatory reaction, just as it can abolish the systemic evidences of infection such as fever and leukocytosis. If this is true it will be a new and rather ominous handicap for the pathologist.

The large size of this heart is one very puzzling feature. Assuming that the patient did have a myocarditis, I would gather from the history that

FIGURE 4.

it had only been present for a few weeks, and I doubt if that would be a sufficient length of time to have caused hypertrophy to a weight of 750 gm. I would be inclined to assume that there must have been enlargement of the heart due to some other cause. The history suggests at least one possibility concerning that, although not very definitely. Whenever this man did not feel quite so well he resorted to 10 or 15 beers. In Germany there is a very well known condition of which I was shown numerous examples some thirty years ago — I have never seen it in this country: the "beer drinker's heart," weighing up to 1000 gm. These men commonly have the history of consuming anywhere from 15 to 20 liters of beer per diem. I know nothing about the clinical picture that these men present. It is my impression that they most often die of intercurrent disease, not of cardiac failure, and that the hearts on microscopical examination look perfectly normal.

Another possibility is that this heart represents the so-called idiopathic hypertrophy and that these foci of necrosis, which were more conspicuous in the inner third of the myocardium, were ischemic in origin, the coronary circulation being inadequate with so large a heart to reach the inner part of the myocardium.

DR. BLAND: Were the lungs all right?

DR. MALLORY: There was one small infarct but no large pulmonary emboli.

DR. DEXTER: What was the interpretation of the cause of death, Dr. Mallory?

DR. MALLORY: The lungs were very heavy, weighing 1800 gm. (about 3 times the normal size) and showed extensive pulmonary edema with hemorrhage into the alveoli; this undoubtedly accounted for the hemoptysis and the immediate cause of death. This was superimposed on a severe chronic passive congestion with thickened alveolar walls and many hemosiderin-filled phagocytes. The appearance was not unlike that seen in so-called "rheumatic pneumonitis," but I do not believe we have any evidence for rheumatic heart disease.

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CASE 37292

PRESENTATION OF CASE

A forty-five-year-old woman entered the hospital complaining of pain in the posterolateral aspect of the right buttock.

The difficulty commenced seven to eight years before admission, when the patient, who had been perfectly well previously, noted a dull ache over the right gluteal region. X-ray films taken at that time showed small cysts in the hip region. The condition was treated with local novocain injections, but the symptoms did not subside. The patient was sent to another hospital, where she reported that a diagnosis of tuberculosis of the hip was made. No treatment was prescribed, but she was referred back to her local physician. Despite continued weight-bearing activity the symptoms of muscle ache and the pain over the buttock disappeared, as did the previous transient pains in the knee and ankle. However, discomfort persisted on bending, walking and changing the position of the leg. Prolonged weight-bearing affected the hip adversely, causing a noticeable limp when she walked a distance. Recent tenderness in the region of the groin was observed.

The patient gave no history of other joint pain or symptoms. At the age of eleven years she was struck by an automobile, but injury to the hip was not recalled. There was a history of scarlet fever but no personal or family history of tuberculosis.

Physical examination showed a well developed and well nourished woman, who had three-eighths of an inch of shortening of the right lower extremity,

which when held in maximum comfort was slightly flexed and adducted. The right thigh measured 17¾ in. in circumference and the left thigh measured 19¾ in. Slight sensitivity over the right mid-Poupart ligament was observed. Limitation of activity of the hips was noted, with the following movements recorded: right flexion 110°, left 145°, right extension −25°, left 0°, right abduction −10°, left 35°, right adduction 20°, left 10°, right internal rotation 20°, left 15° and right external rotation −5° and left 40°.

The temperature was 99°F., the pulse 80 and the respirations 20. The blood pressure was 140 systolic, 85 diastolic.

Urinalysis was negative. The white-cell count was 5400, with 60 per cent neutrophils, 33 per cent lymphocytes, 3 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils. The sedimentation rate was recorded as 3 mm. in fifteen minutes, 11 mm. in thirty minutes, 18 mm. in forty-five minutes and 24 mm. in sixty minutes.

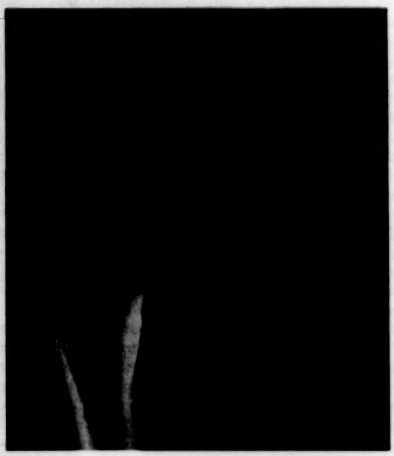

FIGURE 1.

An x-ray film of the chest showed heart, lungs, aorta and diaphragms within normal limits. Films of the left hip were reported normal. The right hip demonstrated extensive changes, with marked narrowing of the joint space and multiple cystic cavities visible both in the femoral head and in the supra-acetabular portion of the ilium. The joint surfaces were irregular and hypertrophic. Spurring had developed laterally (Fig. 1).

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM S. CLARK*: This forty-five-year-old woman had pain in the region of the right hip for a period of eight years, with x-ray changes but without any evidence of systemic disease. In the protocol the only report indicating that this may have been related to a generalized disease was the low white-cell count with a relative increase in lymphocytes. The joint involvement seemed to be confined entirely to the right hip, although she had slight pain in the right knee and right ankle. The problem in this case concerns the differential diagnosis of monarticular joint disease.

May we proceed with the showing of the x-ray films to get a better idea of the anatomic nature of the disease?

DR. JAMES J. MCCORT: The chest examination is negative. The two films of the right hip taken two and a half years before admission show marked narrowing of the joint spaces, irregularity of the articular surfaces — the adjacent acetabulum is irregular — and radiolucent areas within the bone of both acetabulum and femoral head. Lipping is present on the superior margin of the joint. The films taken in the hospital two and a half years later show very little evidence of progression of those changes (Fig. 1).

DR. WALTER BAUER: Was a skull film ever done?

DR. MCCORT: No.

DR. BAUER: Did the patient receive radium water eight years ago?

DR. TRACY B. MALLORY: I am quite sure she did not, Dr. Bauer.

DR. CLARK: It may not be safe to assume that the hip disease was not a part of a systemic disease, but I should like to table that problem and consider the x-ray findings in the hip. The films show marked changes well confined to the skeletal structures adjacent to the joint. There is loss of bone substance, giving a cystic appearance. The loss of bone was due either to replacement of bone by radiolucent soft tissue or to rearrangement of the bony architecture such as one sees in severe degenerative joint disease. The integrity of the articular surfaces is well preserved. There is no flattening of the femoral head, and the joint space is still evident. From these films the best hypothesis is that the bone has been replaced by soft tissue. Usually, at this stage of degenerative joint disease, one sees other changes, namely, sclerosis in the weight-bearing areas of the acetabulum and the head of the femur, with loss of contour. Here one can see considerable new-bone formation, at the acetabular margin, which has taken the form of a spur. It does not have the shape of a smooth periosteal reaction.

*Assistant physician, Massachusetts General Hospital.

On the basis of the protocol I shall assume that the disease was confined to the hip. There are systemic diseases, such as Gaucher's disease, that can produce this picture, but I should not expect it to be an isolated finding in one joint. There should be some other evidence of it, such as splenomegaly. X-ray films of other skeletal structures are not available, and there might have been widespread skeletal disease, but I am going to assume there was not.

In making a diagnosis of monarticular joint disease one frequently follows statistical lines. The infectious arthritides, be they acute or chronic, are usually monarticular. Since an accurate diagnosis is so necessary for their treatment in this situation, one is obliged to consider that diagnosis and to rule it out. If one can adequately rule out infectious arthritis as a cause of this type of destructive joint disease, — and this is difficult, — then one must consider the possibilities of a neoplastic process and of rheumatoid arthritis. I think the latter possibility can be discarded and the discussion confined to whether this was chronic infection or a neoplastic process.

Tuberculosis characteristically starts in the epiphysis, and very large areas of granulomatous tissue can grow from foci in this region. This can result ultimately in large areas of destruction, and we are taught that it characteristically spares the cartilage. As a result of subchondral destruction the cartilage may lift off, but joint narrowing is not an early feature of the disease. I do not think I can say it was not tuberculosis; that diagnosis had already been made once. From the nature of the destructive process and the good preservation of the articular cartilage, I should be inclined to eliminate that possibility. If that was entertained in the clinical diagnosis, I cannot understand why tuberculin tests were not done. If there is any reason to believe that a person has tuberculosis, they certainly should be done. If they are positive in a high dilution, in spite of the fact that the anatomic picture may be bizarre, it still has to be seriously considered. That leaves me trying to explain everything by a neoplastic process.

I think I can discard the usual tumors that would occur in bone — the sarcomas, metastatic carcinomas and myeloma. One would not expect a sarcoma to begin on both sides of the joint at the same time; one would not expect metastatic carcinoma, multiple myeloma and other tumors that have widespread skeletal involvement to be so sharply localized in the joint.

There is a tumor that we occasionally encounter that is called giant-cell tumor of the synovia, which could result in this type of joint disease. Some will not accept this lesion as a neoplasm. They consider it an inflammatory process and call it pigmented villonodular synovitis. For those who might be confused by this terminology, let me digress a moment. As far back as 1865 tumors of the synovia had been described that had giant cells — large polyhedral cells — and lipophages heavily laden with hemosiderin. These tumors have been known by many names, the most common of which has been giant-cell tumor of the synovia. Jaffe, Lichtenstein and Sutro[1] concluded that these lesions were more likely inflammatory than neoplastic. Jaffe advocated the term "pigmented villonodular synovitis"; "synovitis" to indicate the inflammatory nature; "pigmented" because they are grossly brown or yellow; and "villonodular" because they are characterized by fairly large nodules.

Tumors of this type, as we have seen them, have been responsible for a widespread destructive process of the bone in the region of the joint such as this case presents. When I first read the protocol pigmented villonodular synovitis was my first choice, but I am not too happy about making that diagnosis in view of the x-ray findings. As a matter of fact, I cannot make a diagnosis, — and I shall cite pigmented villonodular synovitis as a likely possibility because of the lack of systemic evidence of tuberculosis and because the x-ray findings were not consistent with that diagnosis.

DR. MCCORT: Dr. Bauer, I wonder what prompted you to ask about the radium water? I have the impression that this patient did get x-ray treatment eight years ago.

DR. BAUER: Because of the punched-out nature of the lesion. The only difference between this lesion and one due to radium is the degree of sclerosis around the cystic area. I have never seen a lesion due to radium poisoning in this area of the skeletal system. However, we do not always take x-ray films of the entire skeleton in patients exhibiting the characteristic radium-poisoning lesion of the skull. The degree of sclerosis present permits one to argue that this is not due to radium poisoning or x-ray therapy. It is, however, very important to realize that x-ray therapy is not without harm to the joints, particularly if it is administered repeatedly.

I agree with Dr. Clark that this lesion is not due to tuberculosis, for the reasons he has stated. The amount of new-bone formation, particularly the marginal lipping of the acetabulum, is not seen in tuberculosis. As to the exact nature of the lesion, I agree with Dr. Clark that it is difficult to be certain. My first reaction was that this was another instance of pigmented villonodular synovitis.

Dr. Clark did not mention that some people classify this lesion as a sclerosing hemangioma. This terminology appeals to me as descriptive of the probable nature of the lesion for two reasons: Patients with this lesion do reasonably well after resection, and they also do well with x-ray radiation. I remember only one case of villonodular synovitis of the hip. Dr. Smith-Petersen sent us the sections, which we eventually sent to Dr. G. A. Bennett.

The diagnosis of villonodular synovitis was concurred in by him, although the amount of tissue we had for examination was very little. In the latter case there was also a lesion on the other side of the acetabulum. I do not know whether there is such a thing as a sclerosing hemangioma distinct and separate from pigmented villonodular synovitis, but if there is, I would place this diagnosis even ahead of pigmented villonodular synovitis.

DR. JACOB LERMAN: I should like to ask Dr. Clark if the pain was a prominent enough feature in this patient for a diagnosis of villonodular synovitis.

DR. CLARK: Pain is a consistent feature, but it is not necessarily severe. This patient always had pain.

DR. BAUER: The pain can be intermittent and may only be present when the patient experiences "apoplexy" of the joint. We have come to speak of the rather hemorrhagic effusion of pigmented villonodular synovitis as apoplexy of the joint involved, most commonly the knee. I have made the diagnosis of pigmented villonodular synovitis preoperatively on only one occasion. Dr. Clark and Dr. Ropes have made the diagnosis preoperatively with some regularity.

DR. CLARK: Actually we have only been able to make the diagnosis preoperatively when we have had characteristic synovial-fluid findings, in which a fairly high red-cell count is found. Perhaps Dr. Ropes will comment on that.

DR. MARIAN W. ROPES: Yes; I agree, with the one exception that in one case we had in addition cells laden with fat, which in a rare instance may aid in the making of the diagnosis.

CLINICAL DIAGNOSIS

Degenerative arthritis, with cystic formation in hip.

DR. CLARK'S DIAGNOSIS

Pigmented villonodular synovitis.

ANATOMICAL DIAGNOSIS

Pigmented villonodular synovitis.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The diagnosis we made was pigmented villonodular synovitis, in entire agreement with what Dr. Clark has prophesied. Perhaps Dr. Vickery can tell us what he saw when the joint was opened.

DR. AUSTIN L. VICKERY: When I entered the operating room Dr. Smith-Petersen had just exposed the joint but had not opened the capsule. It appeared somewhat distended, and on incision there oozed from the incision several long, thick, strand-like bits of soft brownish-red tissue speckled with gold. A frozen-section preparation was confirmatory of the entity described as pigmented villonodular synovitis. In addition, the joint surfaces and the synovial surfaces were thickened and quite irregular in outline. The operation consisted of a cup arthroplasty after excision of the synovial tabs and a filling in of the cystic area in the superior posterior acetabulum with bone grafts.

DR. MALLORY: Dr. Bauer has already mentioned some of the conflicting views about the nature of the condition. I can add very little to his discussion. It cannot be considered simply a reaction of the synovia to hemorrhage, since lesions of this sort do not appear in hemophiliacs. To my eye the histologic picture is not that of a neoplasm, although some people have considered it as such and after synovectomy recurrences have been noted. On occasion the recurrences have been frankly neoplastic. However, that would not necessarily prove that the original lesion was neoplastic. The histologic picture is closely similar to that seen commonly in tendon sheaths, especially of the fingers and toes, and is usually diagnosed as benign giant-cell tumor of tendon-sheath origin. The presence of many large giant cells of the foreign-body type and of macrophages filled partly with iron pigment and partly with cholesterol esters and a marked tendency to hyalinization of the connective-tissue stroma are very characteristic features. In what way this lesion of the synovia produces cystic foci of destruction in the surrounding bone is not clear. In our own experience the material we have been given for examination has never included the bone cyst.

Some of you may remember an almost identical case presented here in 1944,[2] which also occurred in a young woman and involved the hip joint, whereas the joint most frequently affected is the knee. Jaffe has also noted in his series of 50 cases that the condition was much commoner in males than in females. It is almost always seen in young persons, — between 20 and 30 being the characteristic age period.

DR. R. C. TEFFT: What happens to the x-ray picture of the bone cysts after the synovectomy?

DR. MCCORT: I cannot answer that; I have not seen enough cases.

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1. Jaffe, H. L., Lichtenstein, L., and Sutro, C. J. Pigmented villonodular synovitis, bursitis and tenosynovitis. *Arch. Path.* 31:731-765, 1941.
2. Case Records of the Massachusetts General Hospital (Case 30131). *New Eng. J. Med.* 230:409-412, 1944.

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GOODBYE, MR CHIPS?

Much has been written and more said about the status of medical education in this country, all of which has emphasized the tremendous cost of producing a doctor of medicine. When these expenses are analyzed by the most ordinary bookkeeper it becomes evident that the money devoted to support instruction, as opposed to other necessary activities of a medical school, is small. Perhaps it is fair to say that teaching expenditures do not exceed 50 per cent of the budget in our better schools.

Money designated for instructional salaries, moreover, is not always rightfully spent, as too much of the time of many full-time teachers is given to research and the care of patients. There can be no question that research, care of patients and administration of hospital services are a necessary part of a teacher's life and contribute greatly to the over-all excellence of the medical school and instruction, if properly apportioned in a teacher's daily hours. On the other hand, medical education in the form of instruction to students is suffering from the emphasis placed on the importance of achievements in fields other than teaching.

William Osler might have a difficult job in securing a professorship today if he were judged solely by the type of work he produced, — although it is obviously unfair to make this comparison between the standards for professorship in clinical subjects today as compared with those of forty years ago. Yet the fact remains that the ability to teach receives insufficient kudos today. The young man who aspires to become a teacher believes only that in order to succeed he must become proficient in something besides teaching; that he must produce in research; and that only through this channel can he succeed.

In the selection of teachers and professors little attention, unfortunately, is given to merit in teaching. The candidate's name must be well known, and he must show promise of a great future in a line of endeavor that, although important, cannot fundamentally be viewed as a good basis for his selection as a teacher. It seems to be the belief that good teachers can be had for a dime a dozen and that good teaching goes hand in hand with other attainments, which, while it may be true to some extent, may not be sound in the long run. How can a teacher devote his best energy to teaching when he knows that other considerations shape his destiny more importantly? It is not only that personal achievement may perish if he fails to pursue his avocation with vigor: the reputation of his school may also suffer.

Medical schools are in competition with each other for attainments in medical research. Those that do best in this field get the best students, who become the mainstay of the institution's reputation. Is this the best system? History will tell us that it probably is not. Is it not possible for a good clinical teacher to be recognized in the same light as another man whose original contributions have brought

him to eminence? It seems at present that it is not possible. Both money for instruction and status for the instructor are needed in this complex society of medical-school teaching if we are not to confuse fundamental issues.

HALL OF FAME

DURING the course of its long history, approximately coexistent with that of the American republic, the Massachusetts Medical Society, fashioned along similarly democratic lines, has prospered under the guidance of no less than sixty-nine presidents.

These past presidents of the Society thus outnumber those of the United States by more than two to one — but they have been elected for shorter terms, having had other things to do. The physicians of the Commonwealth have not wanted to wear their presidents out, or tire of them; there has been also the belief that the Society should spread its honors to include as many as possible of those who are deserving of them.

In the past twelve months, as the Society acquired and prepared to occupy its new home, its executive secretary, Mr. Robert St. B. Boyd, who has come to be identified with the Society as closely and as warmly as any of its physician-fellows, has voluntarily assumed a new and interesting obligation. This activity, which has acquired the urgency and importance of a hobby, has been the collection of the portraits of this long line of presidents, from Edward Augustus Holyoke of Salem, who became the Society's first chief executive in 1782, to the present respected incumbent of the office.

The story of the search, however, which has resulted in the apprehension and taking into custody of the portraits of all but one of these pictorial fugitives, is told by Mr. Boyd himself in the correspondence column of this issue of the *Journal*. A prominent place in the Society's headquarters will be designated and dedicated as its Hall of Fame, and thereafter Mr. Boyd will be under the necessity of acquiring only one new portrait each year to keep the collection up to date.

DEACONESS HOSPITAL CANCER RESEARCH INSTITUTE

Dedication exercises for the New England Deaconess Hospital Cancer Research Institute and the Elliott P. Joslin Auditorium were held on Tuesday, June 5, at the Institute's new building, 194 Pilgrim Road, Boston.

The main feature of the morning program was an address by Sumner T. Pike, vice-chairman of the United States Atomic Energy Commission.

At the scientific session held in the afternoon the principal addresses were delivered by Dr. Sidney Farber, professor of pathology, Harvard Medical School at Children's Hospital, and scientific director of the Children's Cancer Research Foundation; and Dr. Shields Warren, director of the Division of Biology and Medicine, United States Atomic Energy Commission, pathologist of the New England Deaconess Hospital, director of the Cancer Research Institute, and professor of pathology at Harvard Medical School, who spoke on "Scientific Aims of the Cancer Research Institute."

The principal paper of the evening program was presented at the dedication of the Elliott P. Joslin Auditorium by Dr. Charles H. Best, director of the Banting-Best Department of Medical Research, University of Toronto, on "Medical Research and World Health."

The Institute combines under one roof cancer research, atomic research, cancer control and cancer diagnosis, as well as outpatient-department

tumor clinics and postgraduate medical instruction in cancer.

The research activities, which will cover a wide range of interests, will include biologic chemistry, biophysics, biostatistics, clinical contacts, experimental pathology, hematology, radiobiology and x-ray diffraction.

In addition to the research laboratories and the administrative offices, the Institute will house the Cancer Control Unit of the Harvard School of Public Health; the Massachusetts State Tumor Diagnosis Service; the Laboratory of Pathology of the Harvard Cancer Commission and an auditorium for the use of the staffs of the New England Deaconess Hospital and the Cancer Research Institute.

CUSPIDEIRA

A LETTER from a Hungarian reader, appearing in the *Lancet* of May 26, 1951, comments on the previously expressed need of a better term for the new operation, "valvulotomy." Neither "valvulotomy" nor "commissurotomy" seems quite adequate to the needs of the occasion, and the correspondent suggests, among others, the term "cuspidotomy."

As applied to the cusps of a valve the suggestion seems thoroughly logical. To those aging Americans who can still recall some of the adolescent vulgarities of their country's robust youth the term must unfailingly call to mind the cuspidor, that brazen symbol of the days when every hotel lobby was a segment of the nation's frontier.

The elegance of the word, in contrast to the more forthright "spittoon," suggests that even in those rude days an innate refinement was struggling to the surface. This bit of gold among the dross has been immortalized in the nostalgic folk song, "Say cuspidor and not spittoon; Spit not too late nor yet too soon," and so forth.

In order to correct any false etymologic impressions that may be gained but should not be carried away, it must be stated that "cuspidor" has no real or implied relation to the valves of the heart. The word comes from the Portuguese *cuspir* (to spit). There is no implication, however, that the lines quoted above have any reference to "Sonnets from the Portuguese." They are by another, if unknown, author.

A young lady in Cincinnati has been in the habit of twisting and tying her hair so tightly that the scalp had become parted from the skull, and it was found necessary to open the scalp to remove the matter which had accumulated beneath.

Boston M. & S. J., *July 23, 1851*

MASSACHUSETTS MEDICAL SOCIETY

NOTICE

By a vote of the Council, the Secretary of the Society is authorized to maintain a list of fellows of the Society who would be willing to act as witnesses for the defense in malpractice suits against fellows of the Society.

Fellows willing to be placed on such a list should communicate in writing with the Secretary.

H. QUIMBY GALLUPE, *Secretary*

DEATHS

FLEURY — Oswald T. Fleury, M.D., of Holyoke, died on March 1. He was in his fifty-seventh year.

Dr. Fleury received his degree from Tufts College Medical School in 1919. He was affiliated with Holyoke and Providence hospitals and was a fellow of the American College of Surgeons and the American Medical Association.

His widow, a daughter, six brothers and two sisters survive.

IERARDI — Philip A. Ierardi, M.D., of Lowell, died on July 6. He was in his thirty-fifth year.

Dr. Ierardi graduated from Tufts College Medical School. He was a member of the staffs of three Lowell hospitals.

His parents, his widow and three children survive.

PARSONS — Frank S. Parsons, M.D., of Dorchester, died recently. He was in his eighty-ninth year.

Dr. Parsons received his degree from New York University Medical College in 1886.

A son and two daughters survive.

RICHARDSON — Ira W. Richardson, M.D., of Wakefield, died on July 1. He was in his sixty-fourth year.

Dr. Richardson received his degree from Harvard Medical School in 1915. He was chief of the medical service of Melrose Hospital and had been Wakefield school physician since 1944. He was a past president of the Middlesex East District Medical Society and a fellow of the American Medical Association.

His widow and three daughters survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MAY, 1951

Résumé

Disease	May 1951	May 1950	Seven-Year Median
Chancroid	4	0	2
Chicken pox	1844	1865	2228
Diphtheria	11	13	21
Dog bite	1633	1484	1289
Dysentery, bacillary	3	6	6
German measles	745	522	199
Gonorrhea	169	175	273
Granuloma inguinale	0	0	0
Lymphogranuloma venereum	1	0	0
Malaria	6	0	10
Measles	2387	2312	2327
Meningitis, meningococcal	10	5	5
Meningitis, Pfeiffer-bacillus	6	3	3
Meningitis, pneumococcal	5	3	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	1	1
Meningitis, undetermined	7	7	3
Mumps	1849	994	1095
Poliomyelitis	1	0	1
Salmonellosis	11	11	6
Scarlet fever	518	693	851
Syphilis	188	95	279
Tuberculosis, pulmonary	192	193	234
Tuberculosis, other forms	16	13	18
Typhoid fever	2	1	2
Undulant fever	0	0	4
Whooping cough	146	657	495

Comment

Noticeably above the seven-year median for May are German measles, meningitis, mumps and salmonellosis.

The diseases with prevalence below the seven-year median for the month are chicken pox, diphtheria, scarlet fever, undulant fever and whooping cough.

Meningococcal meningitis is the highest for the month since the wartime outbreak.

The eleven cases of diphtheria are the fewest reported for this month in the past seven years; a lower number of cases of scarlet fever has been reported only once since 1918; whooping cough is the lowest ever reported except in 1948.

The incidence of bacillary dysentery is the lowest for this disease in May since 1941.

Geographical Distribution of Certain Diseases

Anthrax was reported from: Haverhill, 1.

Diphtheria was reported from: Arlington, 1; Boston, 3; Brookline, 1; Lawrence, 1; Medford, 2; North Attleboro, 1; Salem, 1; Weymouth, 1; total, 11.

Dysentery, bacillary, was reported from: Belchertown, 1; Camp Edwards, 1; Worcester, 1; total, 3.

Encephalitis, infectious, was reported from: Greenfield, 1; Watertown, 1; total, 2.

Hepatitis, infectious, was reported from: Camp Edwards, 3; Newton, 1; total, 4.

Malaria was reported from: Murphy Army Hospital, 6.

Meningitis, meningococcal, was reported from: Boston, 1; Fall River, 1; Fitchburg, 1; Ipswich, 1; Lawrence, 1; Lexington, 1; Medford, 1; Salem, 1; Springfield, 1; West Springfield, 1; total, 10.

Meningitis, Pfeiffer-bacillus, was reported from: Andover, 1; Arlington, 1; Chicopee, 1; Hull, 1; Peabody, 1; Weymouth, 1; total, 6.

Meningitis, pneumococcal, was reported from: Grafton, 1; North Andover, 1; Townsend, 1; Wakefield, 1; Worcester, 1; total, 5.

Meningitis, mumps, was reported from: Boston, 1; Scituate, 1; total, 2.

Meningitis, undetermined, was reported from: Camp Edwards, 2; Lawrence, 1; Quincy, 1; Revere, 1; Sterling, 1; Worcester, 1; total, 7.

Poliomyelitis was reported from: Somerville, 1.

Salmonellosis was reported from: Boston, 1; Chelsea, 1; Everett, 1; Malden, 4; Marblehead, 2; Medford, 1; Otis, 1; total, 11.

Septic sore throat was reported from: Adams, 3; Boston, 5; Fall River, 1; Lynn, 1; total, 10.

Tetanus was reported from: Athol, 1; Milford, 1; total, 2.

Trichinosis was reported from: Boston, 1.

Typhoid fever was reported from: Millbury, 1; Sutton, 1; total, 2.

CORRESPONDENCE

PORTRAITS OF THE PRESIDENTS

To the Editor: For some years, I have regretted that the Massachusetts Medical Society had no pictures of its past presidents. Accordingly, last fall, when it became evident that we were to have a headquarters building of our own with a place to display these portraits, I embarked on a search for them.

Beginning with Edward Augustus Holyoke of Salem, the first president, who was elected in 1782, and including the present incumbent, sixty-nine physicians have held that office. I hoped that portraits of half this number might be obtained to start a collection that could be carried on for the future.

My greatest hopes, however, have been exceeded, and I now have pictures of sixty-eight of the sixty-nine past presidents. I wish that space permitted me here to thank each of the many persons, including physicians, laymen and officers of institutions, who have furnished help.

The collection naturally started with the easily obtainable pictures of the living past presidents but was soon augmented by a gift from the Harvard Medical School of some sixteen pictures. These were largely of early presidents, whose pictures would have been difficult to obtain in any other way.

With such an auspicious beginning, I was encouraged to call on sons, daughters, grandsons and granddaughters for portraits of their forebears, and everyone to whom I appealed furnished the desired pictures. Copies were made of portraits in the Essex Institute in Salem, the Beverly Historical Society, the Lowell City Hall, the Concord Antiquarian Society and the Massachusetts Historical Society.

From the above sources I received sixty-seven out of the total of sixty-nine. I was ready to admit failure on the last two, until a few days ago my attention was called to a similarity in names between the president of 1798 and an elderly gentleman living on the North Shore. I wrote to him, and today his reply came: "You came to the right man — he was my great-grandfather. I have a miniature which I shall be glad to loan to you — but for God's sake take good care of it."

This gives us sixty-eight out of sixty-nine. The missing one is Dr. William Kneeland of Cambridge, who was born in 1742 and died in 1788 at the age of 46. He was the second president, — from 1784 to 1786. Since Burrage's *History of the Massachusetts Medical Society* says of Dr. Kneeland that "he never attended a meeting of the Society while president," perhaps we shall have to continue without his presence.

I wish again to thank all those who made this collection possible, and to invite them, as well as all the members of the Massachusetts Medical Society, to visit the collection on the third floor at 22 Fenway.

Robert St. B. Boyd
Executive Secretary, Massachusetts Medical Society
Boston, Massachusetts

FILING OF JOURNALS

To the Editor: I have found a very convenient and economical method of filing the several hundred *Journals* that have accumulated during the past few years. Some of your other readers might be interested. The advertising pages in the front and back are removed readily. Each journal is then perforated so that it will fit in an ordinary three-ring notebook. These may be bought in any five-and-ten-cent store for about thirty cents. Each binder will hold about thirteen issues, or one half of a volume. This method

is cheap (about 60 cents and a little time for each volume) and is convenient, since the issues are removable.

I have also kept one binder for the separate index pamphlets, and all indices are filed in this container. When I want to look up an article I can check the index binder and find where the particular article is located.

DON V. HATTON, M.D.

Oak Hill, West Virginia

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Research in Binocular Vision. By Kenneth N. Ogle, Ph.D., Section on Biophysics and Biophysical Research and research consultant, Section on Ophthalmology, Mayo Foundation and Mayo Clinic, Rochester, Minnesota. 8°, cloth, 345 pp., with 182 illustrations. Philadelphia: W. B. Saunders Company, 1950. $7.50.

This monograph is comprehensive in its scope. The material is arranged in four parts as follows: the organization and sensory co-operation of the two retinas; the fusional processes in binocular single vision; the problems in binocular vision when changes are made in the relative magnifications of the two eyes; and the experimental and theoretical bases for aniseikonia. An extensive bibliography concludes the text, and there is a good index. The book is well published and should be in all collections on ophthalmology and optometrics.

Introduction to the Regulation of Blood Pressure and Heart Rate. By Corneille Heymans, M.D., professor of pharmacology, University of Ghent, Belgium. 8°, cloth, 60 pp., with 25 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $2.00.

This monograph presents a study of the blood pressure and heart beat based on the recent literature. There is a bibliography of 55 references. The printing was done by lithography. The monograph because of its reference value should be in all collections on cardiology.

Los Angeles County Hospital, House Staff Manual. David Hamm, Jr., M.D., editor-in-chief. Sixth edition. 8°, paper, 507 pp. Ann Arbor, Michigan: Edwards Brothers, Incorporated, 1950. $4.12. (Copies obtained by application to House Staff Manual, Los Angeles County Hospital, 1200 North State Street, Los Angeles 33.)

Many hospitals and clinics have their own manuals of procedures. The present manual is extensive in scope, covering the whole field of medicine, surgery and the specialties. The material is well arranged, and there is a comprehensive index. The binding is of the ring type.

Thromboembolic Conditions and Their Treatment with Anticoagulants. By Charles D. Marple, M.D., assistant clinical professor, Division of Medicine, University of California Medical School; and Irving S. Wright, M.D., professor of clinical medicine, Cornell University Medical College, and attending physician, New York Hospital. 8°, cloth, 418 pp., with 25 illustrations and 16 tables. Springfield, Illinois: Charles C Thomas, 1950. $8.50.

This monograph presents a comprehensive survey of the existing knowledge of thromboembolic conditions, and their prevention and treatment with heparin and Dicumarol. The text is divided into eleven sections. The first two deal with thromboembolic phenomena in clinical medicine and the mechanism of intravascular clotting. The remaining sections discuss the use of the anticoagulants. A comprehensive bibliography of 684 references is appended to the text. There is a good index, and the book is well published. It should be in all medical libraries and in all collections on vascular diseases.

Sexual Fear. By Edwin W. Hirsch, M.D., attending urologist, Englewood Hospital, Chicago, Illinois. 12°, 307 pp. Garden City, New York: Garden City Publishing Company, Incorporated, 1950. $3.00.

Dr. Hirsch devotes the first five chapters of his book to the history of sexual life and sexual fear in ancient times. He then discusses the various aspects of sexual fear and its psychosomatic treatment. There is a good index, and the book is well published. It should be in all collections on sex.

Radiation Therapy in the Management of Cancer of the Uterine Cervix. By Simeon T. Cantril, M.D., director, Tumor Institute of the Swedish Hospital, Seattle, Washington. 8°, cloth, 196 pp., with 25 illustrations and 29 tables. Springfield, Illinois: Charles C Thomas, 1950. $5.00. (Publication No. 55, American Lecture Series.)

The author discusses the pathology, spread and complications of cancer of the cervix uteri. The greater portion of the text is devoted to radiation treatment. There are chapters on biopsy and on cancer of the cervical stump, on cancer of the cervix in pregnancy and on the place of surgery in the management of cancer of the uterine cervix. There is a bibliography of 120 references and a good index. The monograph should be in all collections on cancer, gynecology and radiation therapy.

Cybernetics: Circular causal, and feedback mechanisms in biological and social systems. Transactions of the Sixth Conference, March 24-25, 1949, New York, New York. Edited by Heinz von Foerster, Department of Electrical Engineering, University of Illinois. 8°, paper, 209 pp. New York: Josiah Macy, Jr., Foundation, 1950. $3.50.

This conference was devoted to a discussion of four topics: psychologic moment in perception; neurotic, potential and human adaptation; the quantum theory of memory and the possible mechanisms of recall and recognition; and sensory prostheses. The book should be in all collections on physiologic psychology.

Our Rejected Children. By Albert Deutsch. 8°, cloth, 292 pp. Boston: Little, Brown and Company, 1950. $3.00.

In this book is told the story of delinquent children and their institutional care in the United States, both good and bad, at the present time. The book is well published, but an index would have made the material more valuable for reference purposes. The book should be in all collections on delinquency.

Untersuchungstechnik des Chirurgen. By Paul Rostock, professor of surgery, Bayreuth. 8°, cloth, 330 pp., with 147 illustrations. Stuttgart: Georg Thieme, 1950. Ganzleinen DM 24.

This textbook for surgeons covers the whole field of diagnosis of the various fluids and organs of the body. There is a comprehensive index of subjects, and the book is well published. It should prove useful to German-reading physicians.

NOTICES

ANNOUNCEMENT

Dr. Harry L. Fulchino announces the opening of an office at 270 Commonwealth Avenue, Boston, for the practice of obstetrics and gynecology.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 4–8. American Congress of Physical Medicine. Page 238, issue of February 8.

SEPTEMBER 12–14. Biological Photographic Association, Inc. Annual Meeting, Boston.

SEPTEMBER 19. American Medical Writers' Association. Page 1066, issue of December 28.

SEPTEMBER 19–21. Mississippi Valley Medical Society. Page 1066, issue of December 28.

SEPTEMBER 30–OCTOBER 2. New Hampshire Medical Society. Annual Meeting. Equinox House, Manchester, Vermont.

(*Notices concluded on page xvii*)